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APRIL 13, 1960

## PROBLEMS IN TOXICOLOGY

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FEDERATION PROCEEDINGS SEPTEMBER 1960

*Supplement no. 4*

# PROCEEDINGS OF A SYMPOSIUM ON

# PROBLEMS IN TOXICOLOGY

## Held in Chicago, Illinois, April 13, 1960

*Sponsored by*

AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
AMERICAN INSTITUTE OF NUTRITION

*Organized jointly by*

FOOD PROTECTION COMMITTEE, NATIONAL RESEARCH COUNCIL
TOXICOLOGY STUDY SECTION, NATIONAL INSTITUTES OF HEALTH
COMMITTEE ON TOXICOLOGY, NATIONAL RESEARCH COUNCIL

*Supported by*

FOOD PROTECTION COMMITTEE, NATIONAL RESEARCH COUNCIL
TOXICOLOGY STUDY SECTION, NATIONAL INSTITUTES OF HEALTH

*Edited by*

J. M. Coon and Elliott A. Maynard

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# Chairman's remarks

MORNING SESSION

CHAUNCEY D. LEAKE

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WE ARE SUDDENLY REALIZING that our extensive use of chemicals for all sorts of biological purposes has raised a lot of embarrassing practical problems. Our industrialization depends on burning enormous quantities of fossil fuels resulting in all sorts of air pollution. Our efforts at pest control seriously threaten the balance of nature. Our industrialization and our sewage disposal contaminate our waters. Radiation hazards from nuclear energy efforts bring fear to people everywhere. In an effort to make our food supply go as far as possible, we are adding all kinds of chemicals to our foods, and we are increasing the number of drugs that we use in a terrifying way. Further, we are using an increasing number of potentially toxic chemicals in various industrial processes.

All of these uses constitute public health hazards, in addition to the terrific imbalance wrought in our natural environment. What are we going to do about these matters? Toxicity is suddenly upon us as a social problem.

It is a wholesome indication of the responsibility of scientists concerned that they should meet together to give public expression to their realization of social toxicology, so that free discussion may result in some sort of effective social control.

# Introduction

R. KEITH CANNAN

*Division of Medical Sciences, National Research Council, Washington, D.C.*

FOR A CENTURY the guardians of the public health have labored to recognize and control the microbiological enemies that pervade man's environment. Only in the last decade or so has the student of preventive medicine begun to apprehend the full measure of the growing microchemical hazard that is adding a new dimension to the problem of the control of the public health.

Under the momentum of an expanding technology, hundreds of new chemicals, alien to nature, are finding their way into the air man breathes, the water he drinks, the food he eats and, more deliberately, into the drugs that he is persuaded to consume to ease his discomforts.

Our atmosphere is becoming increasingly polluted with the combustion products of industrial furnaces, domestic incinerators and internal-combustion engines. Our waterways are carrying an ever heavier burden of the products and by-products of the synthetic chemical industry and the fabrication of metals. In the past 20 years, for example, the output of pesticides by industry, in millions of pounds per annum, has increased from 8 to 540, of plastics from 150 to 5,000, and of detergents from 15 to 3,000. In the present year we are told that we may expect some 10,000 new compounds to become available in commercial quantities.

How long can we expect with impunity to use our airways and our waterways as sewers for the disposal of industrial and domestic wastes? Hopefully, we have relied on dilution to mitigate the acknowledged hazards. Unfortunately urbanization grows with the expansion of industry and the resulting concentrations of population seriously circumscribe the effectiveness of the principle of dilution. Indeed, man's experience with the fallout



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from atomic explosions drives home the lesson that there are limits to the ability of the globe that he inhabits and the atmosphere that envelops it to dilute out the product of man's unrestrained dissipation of energy.

In respect to the maintenance of the safety of man's food supply, the chief problem is probably the increasing use of chemicals in agriculture in the effort to secure greater productivity. More insidious, however, is the deliberate addition, by the processors of food, of chemicals as preservatives or as coloring matter and of emulsifiers, thickeners, thinners, etc., for the purpose of increased customer appeal.

The output of new drugs by the pharmaceutical industry proceeds at a pace that bewilders physician and public alike. The fact that many of these new drugs have their brief day in the limelight and then pass into the discard suggests that the practice of medicine would suffer little loss and would be saved many disappointments were clinical evaluation and acceptance pursued with more deliberate speed.

And so it goes. The technologist, confident in his power to improve man's relations with his environment, is so busy modifying it, even to the point of devising artificial microcosms in nuclear-powered submarines and space capsules, that he can spare little time to determine the long-term effect of his activities on man's well-being.

How is the toxicologist to keep pace with this multiplication of new hazards? When the presence of a noxious agent has been established and methods for the determination of its concentration and toxicity have been developed he functions with confidence. Tolerance limits may be established and the hazard may then be brought under such degree of control as society may ordain. The problem that evades him, because it is presently only dimly apprehended and is beyond intelligent definition, is that of foreign substances present in the environment in such minute quantities that they defy the ingenuity of the chemist to estimate their amounts or, in many cases, to identify their precise natures. Yet the toxicologist knows from experience that chronic exposure to traces of toxic substances may have untoward effects on health. Unfortunately, the remoteness in time of response to initial exposure obscures the relation of effect to cause. Too often this relation only becomes evident retrospectively when a limited population known to have been exposed at high risk to some particular chemical environment gives statistical evidence of increased morbidity or mortality. At the present time the public, alerted by education in the delayed effects of radiation, is acutely conscious of the danger of chronic exposure to traces of putative cancerogenic agents. What reassurance can we give that may help to avoid the adoption of unreasonably restrictive ordinances?

The Symposium which I am privileged to introduce brings together experts in many areas of toxicology. They will define the emergent problems as they see them, the adequacy of existing tools, and the needs for refinement of techniques. There will surely emerge the conviction that the toxicological resources of the nation are barely adequate to cope with the problems that a civilization molded by a continually expanding technology is likely to face.

As a profession, the pursuit of toxicology lacks strong academic roots, formal educational patterns and appealing career incentives. It has recruited precariously from pharmacology, biochemistry, chemistry and public health. The evident needs of society peremptorily demand that these deficiencies be rectified and that a strongly interdisciplinary profession of toxicology be nurtured so that it may make its proper contribution to the protection of the environmental health of our people. In the *Report to Congress of the Surgeon General of the Public Health Service on Environmental Health Problems* it was encouraging to note the acknowledgment that there is urgent need for a high-level organizational unit to centralize and carry out the total environmental mission of the Public Health Service. A national administrative action in this direction could well provide the incentive to improve the scientific stature and the professional dignity of the avocation of toxicology.

# Our man-made noxious environment

E. M. K. GEILING AND WILLIAM D'AGUANNO
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ENVIRONMENTAL HAZARDS HAVE PLAGUED MAN since the dawn of history. Man's enquiring mind and inventive genius have added new potential hazards to the environment with each succeeding age. The results of researches in every scientific discipline in our society have produced an encompassing complex on man's total ecology.

Were we to describe the many hazards which may be encountered in our everyday living, it would leave us with a very dismal or, shall we say, hopeless outlook on life. We cannot minimize the seriousness of the existing hazards, nor is control of the existing hazards impossible. Price (13) aptly states the situation by reminding us that while the inventions of clever men may threaten the survival of the species there are defenses against the hazards of modern technology. Our health agencies have developed specific programs to control the hazards in the industrial environment. Such programs are a composite of research and education and often involve a high degree of cooperation between several government agencies, industry and individual citizens. In some instances, new legislation may be required to control a given situation or to abate a particular hazard (9).

## RADIATION HAZARDS

Unquestionably, the most important discovery of this century was the successful demonstration that the energy of the atom could be released and controlled. The crucial experiment was planned for many months by a corps of outstanding scientists and under the most stringent security regulations. Success on December 2, 1942, proved the feasibility of splitting the atom and controlling the release of astounding amounts of energy. This epoch-making experiment marks the birth of the 'Atomic Age.' Man was thus suddenly faced with the awesome responsibility of having at his disposal a potential source of energy many million times greater than before.

We must meet the grave challenge of utilizing the products of the atomic age for constructive purposes. Fortunately, it would appear that this challenge is being met, in part at least, as judged by the vast number of research projects in practically every branch of the physical and biological sciences, in human and veterinary medicine, in agriculture, and in many industrial processes.

The potentialities for good are almost boundless; the consequences of the misuse of this enormous source of energy are terrifying. Even the peaceful uses of atomic energy are fraught with danger, and present serious problems. There is enough radioactive waste material in huge steel tanks at five different locations in the United States to cause severe pollution of all the land and water areas of the country (3, p. 159). Fallout, pollution of streams, soils and crops, and disposal of waste products are serious hazards which must be guarded against. Solutions for these problems are being sought by many thousands of scientists (2).

While radiation is probably the greatest cause of concern, it is only one of the many hazards which confront us. The phenomenal growth of the chemical industry has made available thousands of new compounds, many of which are toxic, and new ones are constantly being prepared. Production of new chemicals has increased at an average annual rate of 7% since 1947. This rate surpasses, by far, the impressive average annual increment of 3% for all U.S. production. By mid-1959, the chemical industry ranked fourth in size among all industries in the United States. At present more than 10,000 chemical entities contribute to some 500,000 products that are used industrially to produce innumerable durable and nondurable goods, which are integral components of our environment. Predictions that the growth of this industry will continue at an accelerated rate are supported by information from the Manufacturing Chemists' Association. Expenditures on chemical production and construction of research facilities will be nearly 2 billion dollars during the next 2 years. By 1975 the production index will be 100% higher than it is now. It is not at all unreasonable to expect a proportionate increase in the already impressive 10,000 chemical entities—placing man in an environment of a truly chemical age (10).

The intrinsic injurious properties of many of these chemical agents constitute potentially serious environmental hazards. The readily accessible source of toxic or potentially toxic consumer products is evidenced by the thousands of pharmaceutical preparations, chemical pesticides and household products. Toxicological investigations of many of these have been extensive. However, instances have been reported in which chronic or synergistic effects are apparent only after a product has been marketed for some years.

## ACCIDENTAL POISONING

Within recent years we have become acutely aware of the importance of accidental chemical poisoning as a cause of death and disability, chiefly but by no means exclusively in the home. In 1958, accidental poisoning through ingestion of solid or liquid substances caused 1,429 deaths in the United States. Of this number 422 (approximately 33%) occurred in children under 5 years of age. Aspirin (mostly the candied variety) tops the list. Gases and vapors were responsible for 1,187 deaths. An additional 3,958 deaths occurred following the ingestion of either solids, liquids or gases with suicidal intent (18). At present it is estimated that there are approximately 700 nonfatal poisonings for every fatal case in children. Among this number many children and adults were either crippled or made seriously ill, or required some treatment, either in the home or in a hospital.

The Public Health Service estimates that there are about 600,000 children who accidently swallow toxic substances each year. In the United States there are very few, if any, households which do not have on hand several potentially poisonous preparations. These may be either pesticides (vermicides, rodenticides, herbicides, etc.) cleaning fluids, solvents, paints, deodorants, and the like. These materials may be either solids or liquids or gases. Some are toxic when ingested, others when inhaled or absorbed through the skin (8).

According to the testimony presented at a recent Senate hearing (15) there are over 300,000 toxic or potentially toxic trade-named products on the consumer market. In the case of drugs, pesticides and caustic-containing products, federal law requires that the ingredients be clearly stated on the label. However, cleaning fluids, bleaches, certain soaps, detergents furniture polishes and a host of other hazardous substances and devices used in the home in ever-increasing numbers are at present not subject to the existing federal statutes. (There are a few states which do require informative labeling of such products which are not now subject to federal law (9).)

This very serious problem of improper labeling of hazardous household products developed concurrently with the phenomenal growth of chemistry. Fortunately, there are in Congress several bills aimed at remedying the serious defect in labeling of a large number of household products which are not now required to bear a label listing the ingredients. The United States Senate Bill 1283 was passed by the Senate on March 28, 1960. It is entitled Federal Hazardous Substances Labeling Act (16) and became Public Law 86-613 on July 12, 1960.

## POISON CONTROL CENTERS

The American Academy of Pediatrics sponsored surveys in 1951 and 1952 among its members to ascertain the extent to which poisoning was responsible for accidents in young children. Both surveys revealed that a large proportion of the poison accidents were due to the ingestion of substances that were not intended for oral consumption. These startling facts brought to light the urgent need for an agency to which physicians could turn for obtaining information about the composition of a poison as well as appropriate therapeutic measures. The busy practitioner cannot be expected to be familiar with the composition of all the thousands of available products. In order to aid physicians with this serious problem of accidental poisoning, local Poison Control Centers have been established throughout the United States. The first Poison Control Center was established in Chicago in 1953 under the auspices of the Illinois Chapter of the American Academy of Pediatrics with the active cooperation of the Chicago Board of Health, the Illinois State Toxicology Laboratory, the medical colleges of Chicago and the Secretary of the Toxicology Committee of the American Medical Association. The Chairman of the Chicago Center was Dr. Edward Press (11, 12), who has cooperated actively in the establishment of similar centers in other cities in the United States. Since 1953, the number of Poison Control Centers has increased at a phenomenal rate. As of March 1960, there are over 364 such centers in all but three states in the United States and possessions.

The organization and administration of these centers varies somewhat, but all have certain essential features in common. They usually have 24-hour telephone service and maintain a reference file of information on almost any toxic or potentially toxic product. A physician is on call at all times. The centers keep abreast of current methods of treating poisonings and are able to advise physicians accordingly. Approximately 90% of the centers are located in hospitals usually having resident physicians available at all times. Many centers keep detailed records on all poisoning cases coming to their attention. Follow-up on poisoning cases is often achieved in cooperation with local health departments.

## NATIONAL CLEARINGHOUSE FOR POISON CONTROL CENTERS

The striking increase in the number of Poison Control Centers pointed to the need for a central agency to coordinate the vast amount of information accumulating in the many centers. The American Public Health Association at its annual meeting on November 12, 1956, recommended that a National Clearinghouse for Poison Control Centers be set up by the United States Department of Health, Education and Welfare. This meeting was attended by representatives from Poison Control Centers and from such national organizations and government agencies as the American Academy of Pediatrics, the American Medical Association, the American Pharmaceutical Association, the Food and Drug Administration, the National Research Council, the Children's Bureau and the Public Health Service.

In compliance with this recommendation, the National Clearinghouse for Poison Control Centers was established in Washington, D.C., early in 1957 and was designated

as an activity of the Public Health Service in the Accident Prevention Program. The Director is Dr. Howard M. Cann, a pediatrician. His staff includes an assistant director, Dr. Henry Verhulst, a pharmacist with a wide knowledge of pharmacology and toxicology, a competent secretarial staff and statisticians. In addition, record analysts, an educational specialist and nursing consultants from the Public Health Service work closely with the Clearinghouse. Among the activities of the Clearinghouse are the following: Information on poisons and potential poisons from all possible sources are collected, coded, tabulated and analyzed. Suitable reporting forms are furnished to all local centers. Furthermore, advance information is gathered from industrial and other sources on new products that may be poisonous and on changes in composition of existing products. An indexed card file with pertinent information is distributed to all centers. Additional cards are distributed carrying the latest information on new products, on products that may be used only in specific geographic areas, on discontinued products and on rare substances. A very important contribution to the literature of toxicology is the publication, at frequent intervals, of bulletins that summarize statistics obtained from the many local poison centers, new methods of treatment, interesting case reports and abstracts from medical and toxicological literature on poisoning. The Clearinghouse stimulates epidemiologic research, the development of new treatments for poisonings and studies of the basic mechanisms and metabolism involved in poisoning. It also assists and advises in the organization and establishment of new Poison Control Centers.

The following statement (1) by Surgeon General Burney affords a succinct summation of the role of the poison control movement in the United States. "[The National Clearinghouse for Poison Control Centers] has functioned as a coordinating and research service to hundreds of local centers throughout the nation. It has contributed significantly to the knowledge and efficiency of these centers. The poison control movement has the attributes of a sound public health program. It is locally inspired and locally administered—the community base is solid. It is cooperative in origin and in operation. It is practical. It was developed to meet a real health need and it is meeting that need."

### ADVERSE REACTION REPORTING PROGRAM

The accelerated rate at which new drugs, pesticides and food additives are being introduced calls for the establishment of a rapid and efficient mechanism for reporting adverse effects from drugs and chemicals. Hitherto, the Food and Drug Administration has had to rely on the published literature and sporadic or casual reports from physicians, institutions and pharmaceutical manufacturers to supplement its own small staff in following up on experience with new drugs.

On May 4, 1960, the Food and Drug Administration announced an Adverse Reaction Reporting Program (ARRP) for the reporting of unusual or adverse reactions to drugs. It will be conducted initially in cooperation with a limited number of hospitals selected to represent a cross section of the medical specialties. Where necessary, contracts, providing for reimbursement, may be negotiated with the hospitals (or individual physicians designated by them). As the program develops, it is anticipated that additional hospitals will be included with the aim of establishing nationwide reporting. The project is an outgrowth of a voluntary pilot study carried out during the past 4 years in cooperation with the American Association of Medical Record Librarians, the American Society of Hospital Pharmacists, the American Medical Association, and the American Hospital Association.

The program is designed to develop promptly information concerning the untoward effects of drugs, especially the newer ones. The information will be utilized in the resolution of medical and administrative problems under the Federal Food, Drug, and Cosmetic Act; and will also be made available to physicians.

Prior to release for general use, new drugs are required to be evaluated from the standpoint of safety by the Bureau of Medicine of the Food and Drug Administration. Notwithstanding a most careful check of the submitted data, wide clinical use may bring to light effects not apparent in the initial studies. When these undesirable effects become known, appropriate measures are taken to afford a greater degree of patient protection. Remedial steps necessary on the part of the drug manufacturer or distributor may vary from a change in labeling, and alerting of physicians and others responsible for patient care, to a complete removal of the drug from the market. The program is directed by Dr. Irvin Kerlan, chief of the Research and Reference Branch, Bureau of Medicine of the Food and Drug Administration.

### THE FARMER AND OUR FOOD

The increase in agricultural productivity in this country has had a proportionate impact on our environment. The result is that the role of the farmer has broadened considerably in our society. In 1940 the average farmer produced enough for himself and 10 others; in 1958 he produced enough for himself and 22 others. From 1950 to 1958, farm output rose 20%, while the population increased 15% (10).

This increased productivity is the result of a number of contributory factors. Among them are: *a*) the striking increase in the use of chemicals such as fertilizers, insecticides, fungicides, herbicides, nematocides, coccidiostats, animal health protectants and medicated feeds; *b*) more efficient use of machinery in practically all farming operations; *c*) better seeds and improved strains of practically all breeds of farm animals; *d*) more efficient training of larger numbers of students in our agricultural and veterinary colleges, as well as an increase in the many types of short courses offered to farmers in these

institutions; *e*) contributions for research from federal and state Departments of Health and Agriculture, who also contribute in an advisory and regulatory capacity.

The use of a wide variety of chemicals on the farm has undoubtedly been the most important single factor accountable for the marked increase in raw agricultural products. The toxicological significance of many of these agents is generally recognized. The concern expressed by regulatory officials and their continued emphasis regarding adherence to label warnings and directions is certainly justifiable. The farmer, by disregarding these warnings and directions, can directly expose a large mass of our population to the toxic effects of the chemicals which he uses currently without benefit of special training and without any real appreciation of the problems and dangers of residual contaminants.

## MEDICATED FEEDS

The practice of adding drugs to the feed of domestic animals for both prophylactic and therapeutic purposes dates back many years. It is a simple as well as a convenient method of administering medicaments to large numbers of animals. Two of the main objectives of adding such drugs are to shorten the time required for animals to reach market weight and to increase the efficiency of feed utilization by the animals.

Among the drugs incorporated in the animals' diet for these purposes are: diethylstilbestrol, dienestrol diacetate, iodinated casein, organic arsenicals, antibiotics, nitrofurans, sulfonamides, coccidiostats, organic tin compounds, parasiticides and many others. The widespread use of potent chemical agents introduces additional problems into the protection of the food supply of both man and animals. We are indebted to Dr. Charles G. Durbin, Veterinary Medical Director, Food and Drug Administration, for allowing us to reproduce in table 1 his list of drugs currently added to animal feeds (3). Drug residues which might occur in the edible tissues of animals are increasing in importance and causing a proportionate amount of concern. An example is the use of chicken feeds containing the coccidiostat nicarbazine, which results in the appearance of this drug in the eggs.

The term 'medicated feed' as commonly used is intended to designate a feed to which a drug or drugs have been added. The extent to which this adding of drugs has grown and the complexity of the scientific and technical problems involved indicate that the feed manufacturer is in reality also a drug manufacturer. The addition of a drug to feeds makes the resulting product, in essence, a drug. Such a feed may now be subject to the New Drug as well as to the Food Additive sections of the Federal Food, Drug, and Cosmetic Act.

The large amount of drugs being used in medicated feeds makes the industry 'big business.' For example, the antibiotics used in animal feeds are itemized in table 2. Table 3 shows the output of leading antibiotics. It will be seen that the antibiotics used in the medicated

TABLE 1. *Drugs Currently Used in Animal Feeds*

| Drugs | Withdrawal Times* | Certifiable Antibiotics |
|---|---|---|
| *New drugs* | | |
| Arsenosobenzene | 5 days | Bacitracin |
| Bithionol and methiotriazanime | 3 days | Chlortetracycline |
| Dienestrol diacetate | 48 hr. | Dihydrostreptomycin |
| Diethylcarbamazine (dog food) | | Penicillin |
| Diethylstilbestrol | 48 hr. | Streptomycin |
| Diethylstilbestrol (poultry water) | 4 days | Streptomycin |
| Hygromycin B | | |
| Nicarbazin | 4 days | Enzymes (except pepsin) |
| 2-acetyl-amino-5-nitrothiazole | 7 days | |
| 2,4-diamino-5(p-chlorophenyl)6-ethylpyrimidine | | |
| 3,5-dinitrobenzamide | 48 hr. | |
| Glycarbylamide | 4 days | |
| Hydroxyzine hydrochloride | | |
| Nithiazide | 24 hr. | |
| Nystatin | | |
| Oleandomycin chloroform adduct | | |
| P-ureidobenzenearsonic acid | 5 days | |
| Reserpine | | |
| *Other drugs* | | |
| Acetyl-(p-nitrophenyl) sulfanilamide | 5 days | 4-Nitrophenylarsonic acid |
| Aminonitrothiazole | 7 days | Iodinated casein |
| Arsanillic acid | 5 days | Menadione sodium bisulfite |
| Aterrimin | | Oxytetracycline |
| Cadmium anthranilate | 30 days | Para aminobenzoic acid, sodium or potassium salt of para aminobenzoic acid |
| Di-N-butyltin dilaurate | | |
| Dinitrophenylsulfonylethylenediamine | | Pepsin |
| Dried rumen bacteria | | Phenothiazine |
| Dynafac | | Piperazine |
| Erythromycin thiocyanate | 5 days | Piperazine hexahydrate |
| Furazolidone | | Piperazine monohydrochloride and dihydrochloride |
| 2,2'dihydroxy-5,5'dichlorodiphenylmethane | | Piperazine phosphate monohydrates |
| 3-nitro-4-hydroxyphenylarsonic acid | 5 days | Piperazine sulfate |
| Nicotine | 5 days | Sodium arsanilate |
| Nitrofurazone | | Sodium fluoride |
| Nitrophenide | 4 days | Sodium propionate |
| | | Sulfaquinoxaline |

* Required to free tissues of drugs under specific conditions of use and representation.

TABLE 2. *Antibiotics Produced for Animal Feed Supplements, 1956**

| Antibiotic | Pounds Manufactured | % of Total Output |
|---|---|---|
| Penicillin procaine | 173,455 | 20.5 |
| Streptomycin | 8,250 | 0.9 |
| Bacitracin | 21,104 | 2.5 |
| Chlortetracycline | 465,197 | 54.9 |
| Oxytetracycline | 179,190 | 21.2 |
| Neomycin | 29 | |
| *Total* | 847,225 | 100.0 |

* By 1956 animal feed supplements represented over 27% of total antibiotics output. From (3a).

TABLE 3. *Output of Leading Antibiotics**

| Antibiotic | 1948 *lb.* | 1956 *lb.* |
|---|---|---|
| Penicillin | 155,873 | 1,059,704 |
| Streptomycin | 80,737 | 148,999 |
| Dihydrostreptomycin | 2,989 | 492,173 |
| Chlortetracycline | 661 | 560,663 |
| Oxytetracycline | | 324,614 |
| Tetracycline | | 220,074 |
| All others | 72 | 275,146 |
| *Total* | 240,332 | 3,081,373 |

* From (3a).

feeds industry represents roughly over 27% of the total antibiotic output. The use of these potent drugs in medicated feeds is attended with potential hazards and requires careful observance of the directions for their use. To insure the proper use of a medicated feed, there must be competent personnel to perform each of the following steps in the process of manufacture: *a*) the drug must be checked for purity and weight before use in the premix; *b*) the premix must be properly prepared and assayed; *c*) the final dilution of the premix with the feed must also be checked; and *d*) full directions for use of feed must be clearly stated on the label on the feed container. The farmer in turn must not use the feed for the stated time prior to slaughter (3).

It should be noted that animal feeds may incorporate an additional hazard, i.e. the accidental presence of pesticide chemical residues and other potential toxicants applied to the plants or added to the soil to improve the crop or to protect it against pests.

### THERAPEUTIC USE OF DRUGS IN FARM ANIMALS

In recent years, many new drugs have been introduced into veterinary medicine. It has been estimated that 75 tons of antibiotics are used yearly in intramammary infusion for the prevention and treatment of bovine mastitis, probably the most important economic disease in dairy cattle.

Milk from cows treated with the recommended amounts of penicillin may contain some antibiotic residue up to 72 hours after the last infusion into the udder. For this reason the label is required to include a statement that milk from treated cows must not be used for human consumption for at least 72 hours after the latest administration. Withdrawal time for antibiotics administered parenterally have not yet been established. Studies to furnish the necessary data are still in progress.

Commissioner Larrick, of the Food and Drug Administration, has repeatedly emphasized that the nation's milk supply must be kept free of drugs and pesticides such as penicillin and chlorinated hydrocarbons ('Dairy Products and Additives,' an address delivered at the Dairy Products Improvement Institute, New York City, February 19, 1959). No tolerance above zero has been set for any drug or pesticide in milk. Recently the Food and Drug Administration prepared a milk-check envelope stuffer. This leaflet is an official notice from the United States Government to individual milk producers. It will be sent through the distribution channels of the national dairy organization and other interested groups.

The caption to this leaflet, is printed in bold type, "Keep Residues of Drugs and Pesticides out of Milk." In the body of this notice are specific recommendations for keeping milk safe and pure. The very serious effect of small amounts of penicillin to individuals sensitive to this product cannot be overemphasized (5).

### FOOD PROCESSING

It is not only on the farm that chemicals are being used in the production of our food. Large amounts of chemicals are employed in the food processing industry. Increasingly, the consumer demands more processing of foods before purchase. The trend in modern civilization is toward food prepared for immediate cooking or consumption. A substantial number of chemicals, perhaps 2,500, have been introduced into our food supply to function as preservatives, color-improvers, extenders, flavor intensifiers, texture modifiers and nutritional factors. Even the new types of packaging offer a potential source of food additives in that diffusion of toxic chemicals may occur from the packaging to the food during storage. Many of the chemicals may be of unknown toxicity or even of known high toxicity. Data must be provided that either the chemical does not become a component of food or that it is safe toxicologically in the amounts present.

The Pure Food and Drug Law of 1938 spelled out the requirements for foods and drugs. In essence, it put the burden of proof on the Food and Drug Administration as to whether a chemical could be kept out of food. The Food and Drug Administration had to show, by scientific proof, that a chemical was unsafe before its use in food could be prohibited. Under the Food Additives Amendment of 1958 it became the responsibility of industry to show the chemical was safe before it could be allowed in food. The product, even when safe toxicologically in the amounts used in food, is restricted to the minimum amount necessary to produce the desired effect (17). Data must be provided to show that the desired effect is

actually produced. The fine work done by the Food Protection Committee to protect the American public is worthy of commendation (4).

### AIR POLLUTION

Air pollution has become an exceedingly serious public health hazard in a number of localities in the United States and in most industrial areas throughout the world. The air pollution problem was already prominent in many industrialized cities more than a century ago. The chief pollutant, then, was smoke from coal and wood. However, in the past 50 years industrial production has increased over 900%, and the number of automotive vehicles has increased from 1,000 to 70 million. In the United States, the population has more than doubled and has concentrated to the extent that more than half the population lives in metropolitan areas which cover less than 5% of our total land space. This intense concentration of population, coupled with the tremendous rise in industrialization and increase in the use of automobiles in these areas, has led to an intensification of toxicants emitted into our atmosphere (7). The chief air pollutants today are the oxides of nitrogen and sulfur, the aldehydes, carbon monoxide, smoke, condensed fumes and organic vapors, often referred to as hydrocarbons, of which there are said to be 200 in automobile exhaust fumes alone. Statistical analysis and tabulation of pollutants on a nationwide scale have not yet been undertaken; however, their magnitude can be envisioned by considering the fact that data shown in table 4 are for New York and Chicago only.

Health hazards from air pollution may be of an acute or chronic nature. Acute air pollution episodes of a spectacular nature such as the Donora catastrophe of 1948 are not the most difficult part of the problem. There are more subtle effects which may result in chronic illness, disabilities and/or premature death. Toxicants emitted may act as irritants on mucous membranes, by specific toxic reactions, which may be cumulative by allergenic and possibly by carcinogenic activity. Evidence is accumulating which suggests that air pollution may be involved in the development of chronic bronchitis, asthma, emphysema and lung cancer. Dr. David F. Eastcott, formerly Assistant Director, National Institute of Health of New Zealand, recently stated that "immigrants to New Zealand, from highly industrialized Britain, run a risk of lung cancer 30% greater than persons born in New Zealand of the same stock and way of life. If they are more than 30 years of age on coming to New Zealand, their risk is 75% greater." Similar evidence is available from the Union of South Africa. The serious effects may be discovered only after years of exposure—11 years in the case of the Donora episode.

TABLE 4. *Estimated Amount of Toxicants Liberated Into the Atmosphere in Tons per Day**

| Pollutant | New York | Chicago |
|---|---|---|
| Sulfur dioxide | 2,170 | 3,197 |
| Sulfur trioxide | 133 | 182 |
| Hydrogen sulfide | 133 | 196 |
| Nitrogen oxides (as dioxide) | 1,355 | 1,103 |
| Hydrogen cyanide | 96 | 196 |
| Ammonia | 115 | 141 |
| Hydrochloric acid | 118 | 141 |
| Formaldehyde | 131 | 147 |
| Organics, miscellaneous | 4,330 | 3,836 |
| Organic acids (as acetic) | 1,542 | 1,732 |
| Fluorides (as fluorine) | 8 | 16 |
| Solids (smoke, dusts, etc.) | 12,693 | 26,236 |

* Data from *Literature Review of Metropolitan Air Pollutant Concentrations*, Stanford Research Institute, 1956.

Preliminary data from the Donora incident indicate that the group made ill by exposure to the fog show a higher disease and death rate than do the residents not affected by the fog (14).

The yearly economic losses due to air pollution have been estimated at 7.5 billion dollars. They include: damage to crops, livestock and vegetation; corrosion; soiling; fuel losses; interference with visibility; and interference with production or services (6).

### WATER POLLUTION

The pollution of our water supply is due, in large measure, to the fact that many of our major industries and population centers are located along rivers or inland lakes. The most urgent problem is the adequate handling of the many tons of nonliving contaminants, which are discharged as waste, or otherwise, and find their way into our water supplies. A number of these substances are as yet unidentified chemicals. There are often so many of these products present in a single sample of water, that analysis takes many days of work just to name the broad categories of chemical constituents. A great deal of research needs to be done to identify these contaminants, to determine their pharmacological and toxicological effects, and to develop control methods. It is necessary to formulate the solution of these problems on a broad base, and it requires the collaborative efforts of well-trained scientists, including engineers, biologists, chemists, pharmacologists, toxicologists, physicians and statisticians. Such individuals must have well equipped laboratories in which to carry out their researches.

The presence of radiological waste in some of our rivers, notably the Columbia River, adds a new hazard which, if not checked, may in time become a serious menace (7).

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# Food: additives and natural components

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THE NUTRITION SCIENTIST has usually concerned himself with those attributes of foods which fulfill nutrient requirements. He has clarified the chemistry of nutrients, elucidated the metabolic roles and conversion of these nutrients, described the body economy of particular factors, determined the requirement of various animals for these, and detailed the distribution of nutrients in foodstuffs in order to make possible the application of scientific knowledge in dietary or ration planning. Recognition of and interest in many essentials stemmed initially from diseases of man or animals which could be associated with foods—scurvy, pellagra, rickets, night blindness, anemias, beriberi, hunger edema, kwashiorkor, goiter, 'salt sickness', and so on.

In a few instances attention has initially been directed to a beneficial nutrient as a result of the illness caused by an excessive intake. Thus selenium toxicity among farm animals in the seleniferous areas led workers to regard this element as a toxic or undesirable substance (8) and this attitude may well have discouraged nutritionists from studying whether any levels of the substance might be beneficial. It was recently recognized that selenium in minute quantities is beneficial (18–20). A similar history pertains in the instance of fluorine (16)—first incriminated as an undesirable element in water because the constant use of water containing a concentration of a few parts per million caused mottled enamel and, in higher concentrations, bone disease; later found to be distinctly beneficial in the prevention of dental caries when consumed in small amounts. The acceptance of the beneficial effect of iodine in goiter was delayed for years because of the production of iodism in persons treated with too large doses of the element (see (12), especially p. 251).

The widespread adoption of highly desirable programs of iodinization and of fluoridation has repeatedly been impeded by the opposition of misled zealots who believe "once a poison, always a poison." Such absolute concepts have stifled progress in health throughout history. Reflect, if you will, on the influence of the authoritarianism of Galen.

The above-cited nutrients may be unique either in the relatively small margin of safety between beneficial level and toxic level or the ease with which grossly excessive quantities can be ingested under unusual conditions. However, they are not unique examples of essential nutrients which if ingested repeatedly in unusual quantities become toxic. In man continued gross overdosage with either vitamin D or vitamin A produces the too familiar and sometimes most serious syndromes of hypervitaminoses D (4) or A (11). Cobalt (21) is essential for ruminants and, in the vitamin $B_{12}$ molecule, for man. Cobalt deficiency disease is a well-established syndrome in animal husbandry, yet the chronic ingestion of rather low quantities of cobalt produces polycythemia in animals and man. Grossly excessive intakes of riboflavin (22) or of folic acid (5) lead to renal damage in rats. An excess of lactose in the diet of the young rat produces cataract (15). An overage of calories from any source leads to obesity and its consequences. Excessive intakes of several amino acids have been found to produce toxic syndromes in experimental animals. One could elaborate a long list of such examples but the ones cited suffice to illustrate that sufficiently excessive quantities of essential nutrients are toxic. Additional understanding of these properties is needed and might be of considerable value in the identification of optimal nutrient intakes.

A few years ago this 'toxicity of excess' NaCl was studied in the rat by a group of workers at Vanderbilt University (3, 13, 14). Various dietary levels of common salt were incorporated into a complete, purified diet and fed throughout the life span of the rats. The animals were weighed, blood pressures recorded, and other observations made at regular intervals. In each of several experiments, levels of salt ingestion of 2.8% or greater were associated with elevated systolic blood pressures and the early appearance of hypertension within the (rat) population. The percentage of animals surviving to expected older age was maximum at 0.15% NaCl and decreased sharply as salt was increased to the higher levels. Corresponding differences in average life span were seen. A considerable number of the animals developed lipemia, hypercholesterolemia, lipid deposits in the renal parenchyma and arterioles, and other findings suggestive of similar conditions in man. If one projects these findings to the human intake level one can calculate that the dietary level of 2.8% for the rat is the order of magnitude of intakes common in the human.

Indeed, our experience with salt leads us to suspect that there are many dietary constituents long used in variable quantities in traditional dietaries, the nutritional toxicology of which profitably could be investigated.

Particularly would I point to the variety of condiments regularly used in large amounts in many tropical areas, in Africa, Asia, and some parts of Latin America.

This 'toxicity of excess,' as one may call the above, is apart from another type of effect produced by many foods. Recognized syndromes or pharmacologic effects in man and animals result from the ingestion of excessive quantities of foods which contain biologically active compounds (see (17) for many examples). Uncooked soya contains an antitrypsin which influences digestibility, cotton seed contains gossypol, some nuts and manoic contain cyanide precursors, many of our common drinks (coffee, tea, cocoa, yherba matte) contain well known pharmacologically active compounds. Cereals contain phytate which has been incriminated as interfering with calcification, many commonly eaten vegetables such as rhubarb, spinach, chard and poke contain large amounts of oxalate. In potatoes, solanin may be increased by improper harvesting. Saponins are present in many foods (for example, potato, soya, beet, spinach, bread fruit, peanut, calabash, tomato, orange, etc.). The nature and biologic importance of these have not been established. We accept these foods with little thought and are likely to dismiss consideration of any effect by concluding that the substance occurs in inconsequential amounts—a conclusion less widely accepted for materials, often less suspicious, which get into foods as additives.

Goitrogens are present in many foods. Recognition of this has been widely confirmed since the classical identification of Astwood and co-workers (2) of L-5-vinyl-2-thiooxazolidone as the goitrogen in the rutabaga, rape and other members of the Brassica species. Indeed, Clements and Wishart (6) found that physiologically significant quantities of goitrogenic activity in man are present in the milk of cows grazed on a member of this species, chow-Moellier. The biochemical toxicology of these and other goitrogens assumed added importance in the nutrition field as a result of the use of the weed killer aminotriazole and the unfortunate consequence to the cranberry market in the United States of contamination of some batches of cranberries with this substance. The data on which the decisions were made in this case have not been made public, but Astwood (1) has argued that the antithyroid activity of the most heavily contaminated cranberries was of the order of 1/100 of that normally occurring in the edible portions of Swedish turnips. Does the consumption by the human or other animals of quantities of these agents present in non-contaminated foods exert significant pharmacologic activity? Is there evidence that one of these compounds (naturally occurring or man-made) has some tumorigenic activity which is not exhibited by the others? Surely appropriate metabolic and toxicologic studies can give a scientific basis for answering these questions. One cannot prejudge the answer by legislative action such as the so-called 'Delaney clause' in our present Food and Drug Law.

I have but touched on the vast number of intriguing interests in the toxicology of unprocessed foods. There are many syndromes caused by food toxins: lathyrism, ackee poisoning, epidemic dropsy (caused by argomenone oil), fagopyrism (the photosensitization induced by buckwheat), senecio toxicity, the shellfish alkaloids, mushroom poisoning, bankrek, and the like.

Then there are many other examples of wholesome foods which are relatively high in content of arsenic, copper, zinc, and other materials usually regarded as noxious—noxious, certainly, in physiologically meaningful amounts but not in the quantities usually consumed!

Man's food supply has been extended through the ages by the utilization of more varied food crops and by the improvement of agriculture, storage, preservation and distribution. It has been improved in quality by better food control and sanitation. Continued nutritional betterment of food is occurring through utilization of both agricultural and industrial products. So we find new processes, new additives, new utilization of industrial by-products influencing the food supply. We exist in the midst of a changing food environment—a situation which is new only in that the rate of change is faster than in the experience of our forefathers.

An accompaniment of this change is the appropriate use of food additives—a necessary part of our present state of technologic development. As stated in the first report of the FAO/WHO Joint Expert Committee on Food Additives (9), it is to the advantage of the consumer when food additives are used for the following purposes:

*a*) To maintain the nutritional quality of a food.

*b*) To enhance keeping quality or stability, with resulting reduction in food wastage.

*c*) To make foods attractive to the consumer.

*d*) To provide essential aids in food processing.

But the use of additives is not justifiable (9) when a hazard associated with their use would render the use unsafe, or if the additive is employed:

*a*) To disguise the use of faulty processing or handling techniques.

*b*) To deceive the consumer.

*c*) When the result is a substantial reduction of the nutritive value of the food.

*d*) When the desired effect can be obtained without the additive by good manufacturing practices which are economically feasible.

In evaluating safety the concern should be with the hazard involved in use of the substance—not with man's preconceived classification of the compound.

The study and evaluation of the potential hazard or safety for use of a given additive is a scientific question, not a legal one. The methods of study are those available to biologists and chemists. Only general methodologic guides can be and have been provided by such statements as those of the Food Protection Committee (7), the FAO/WHO Joint Expert Committee on Food Additives (10), and other groups. Stereotyped study plans must not stifle the challenging opportunities for basic scientific investigations of the metabolism, fate and significance of

compounds which may be or may become food additives any more than it should stifle the appraisal of substances present in unprocessed or natural foods. The broad area of food toxicology is ready for a major exploitation by scientists with sufficient imagination and interest to take advantage of the challenging opportunities.

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# Control of toxicity in foods, drugs and cosmetics

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THE FOOD ADDITIVES AMENDMENT was passed by Congress in September 1958 and became fully effective on March 6 of this year. This marks a new era in the control of toxicity in food. Prior to the Food Additives Amendment it was against the law to add a toxic chemical to food unless the necessity of such use could be shown and a tolerance had been set. However, this provided only limited protection, because many of the new chemicals that were finding their way into food were of unknown toxicity, and frequently considerable time would elapse between their introduction and the completion by the Food and Drug Administration of sufficient animal testing to establish their toxic character. The fact that many of the chemicals were closely guarded trade secrets did not help matters either.

Under the Food Additives Amendment all this has changed. Any new compound that is intended for addition to food, or for a use whereby it may reasonably be expected to become a component of any food, must be thoroughly tested to establish the safety of the proposed use. Necessary tests generally include 2-year feeding experiments in two species of animals, preferably rats and dogs over a range of dietary levels which will bring out all the toxic potentialities and also establish the concentration that is completely innocuous to the animals, the so-called 'no effect' level. Blood counts together with gross and microscopic examination of the organs are an integral part of such tests. If it should turn out that the compound under study is capable of producing cancer, its use in food in any amount whatever is prohibited. Otherwise the data from the animal tests serve as a basis for setting a tolerance for the material in food. In setting a tolerance for a food additive, many things are taken into consideration. These include *a*) the probable consumption of the additive and of any substance formed in or on food because of its use; *b*) the cumulative effect of the additive, taking into account any substance already in the diet which could have a similar effect; and *c*) a safety factor to allow both for the difference in susceptibility between man and test animals and also for the varying degrees of susceptibility that can be expected to occur within the human population. Before a tolerance can be set, it is necessary to have a reliable analytical method that can be used for enforcing it.

So much for the new food additives, but what about the host of chemicals already in use when the act was passed? These fall into several categories. Some are covered by prior sanction; that is, there has been a previous official expression of opinion that the particular use is safe. Others are generally recognized as safe (GRAS in the Washington jargon) among experts qualified by scientific training and experience to evaluate their safety. Such an evaluation may be based on scientific procedures, or, in the case of a substance used in food prior to January 1, 1958, it may be based on scientific procedures or on experience resulting from common use in food. All the other chemicals are classed legally as food additives[1] and must have a tolerance established through a regular petition. In many instances an extension for 1 year has been granted in which to complete the necessary tests.

Determining which substances are generally recognized as safe has proved to be a challenging problem. It is not enough that the experts employed by the Food and Drug Administration regard a substance as safe, or that this belief is shared by our people and the scientists who developed and presented the data upon which our opinions were based. Neither is it sufficient to be armed with unpublished data which, if presented to a group of scientists, would support an opinion of safety. We think the facts upon which experts generally can reach their conclusions of safety should be available in the published scientific literature or in other material to which they have free access. Our first step was to prepare a list of substances which we believed appropriately qualified scientists would recognize as safe for the intended use. This list was then circulated to such scientists and their opinions solicited. When the replies were received we were impressed with the high degree of responsibility shown and with the thoroughness of their examination of the list. In general the views expressed confirmed our own. Where there was a significant departure the item was dropped. The remaining compounds have been

[1] A food additive, as defined in the Food Additives Amendemnt of 1958, refers to a substance used or proposed for use in foods, which is not generally recognized as safe for such use by "experts qualified by training and experience to evaluate its safety . . ." On the other hand, the term 'food additive' is widely used in the literature and by workers in the field to refer to a chemical added to foods, whether or not it has been generally recognized as safe.

published in the Federal Register as generally recognized as safe and therefore not subject to the Food Additives Amendment.

The comprehensive character of the Food Additives Amendment is illustrated by the fact that it applies to such diverse materials as the coating on paper plates if it migrates into food, residues in meat, milk or eggs resulting from the use of drugs in farm animals, as well as such intentional additives as ink used to mark prices on fruit and vegetables, emulsifiers, preservatives and radiation. Excluded because they are already provided for elsewhere in the Federal statute are such things as pesticides, occurring in or on raw agricultural commodities, and coal-tar colors.

## TOXICITY IN DRUGS

In contrast to food additives the pretesting of new drugs has been required for over 20 years. This provision in the 1938 Federal Food, Drug and Cosmetic Act was clearly inspired by the Elixir of Sulfanilamide disaster, in which over a hundred persons lost their lives as a result of the distribution of an untested drug containing diethylene glycol as the solvent.

The most serious problem facing those who are concerned with the toxicology of drugs is that of methodology. We have become so occupied in testing the multitude of new drugs that are being developed that we have not taken time out to make sure that the methods we are using are the best that can be devised. In the past quarter of a century there has been virtually no change in the way by which the toxicity of drugs is studied. True, we use larger numbers of animals now, we treat them with the drug for a longer period of time, and we use two species where formerly we were frequently content with only one, but basically the procedures have remained the same. If the results had always been satisfactory, there would perhaps be no reason to consider a change; but too often our animal tests have failed to warn us of such side effects as agranulocytosis or jaundice, or have warned us of trouble that failed to materialize.

There is no clear record of how the present system was arrived at. If one were called upon to justify it, he could mention such points as these: a mammal should be a more promising candidate than one of the lower forms; of the mammals the dog and the rat with their long close association with man, even to the extent of sharing in his food, might be expected to resemble best his reaction to drugs; and finally two species ought to be better than one. However, it is asking too much of the dog and rat to expect them to forecast down to the last detail the toxic side effects each new drug will have in man. It is unlikely that they will detect such complications as, say, Parkinsonism and depression of spermatogenesis with the same competency. The toxicity tests of the future may rely not on one or two such 'general utility' types of animals but rather on a dozen or more 'specialist' types, each one chosen, and if necessary created through selective breeding, for its peculiar capability in detecting the one or two types of toxicity for which it is responsible. Rather than requiring more animals the new system should require less because the 'end point' between effect and no effect will be so much sharper. Tests on tissue cultures or even enzyme systems may have a share too, but only after such problems as absorption, distribution and metabolism have been worked out on the intact animal. There is, of course, the possibility that overspecialization could prove a handicap when a new drug possesses a form of toxicity that does not fall into any of the patterns of the detection system. In such cases, however, the new procedure should prove at least the equal of the current one since some of the many species represented could be expected to be susceptible to the peculiar toxicity involved.

If anyone doubts that such a revolution is on the way, let him look around. He will see that the earliest phases are already here. Ducklings are used to detect cataract-producing drugs, guinea pigs for sensitizers, and special strains of mice for cancer-producing drugs.

Another long-standing problem in the toxicology of drugs is that of interpretation. Having gotten our results in the experimental animals, how do we translate them to man? Fortunately this is one of those problems that get easier with the passage of time. As we accumulate parallel data on man and animals, we learn their respective peculiarities, in response to an increasing number of drugs.

A related problem is one of evaluation. After the side effects have been identified and their severity and frequency in man have been determined, we need to decide whether the benefits of the drug in a particular disease outweigh the harm it is capable of producing. Ultimately this is a decision which the physician must make in the case of each individual patient. Where there is uncertainty it usually results from incomplete information on toxicity. The golden age of toxicology can be said to have arrived when we know all we need to about the drug but must learn more about the disease before we can conclude whether or not the drug is safe enough for use in treating it. Safety is indeed relative. In mild disability even the slightest drug-induced discomfort may be unacceptable. A patient with continued fever may find the diaphoresis produced by aspirin more objectionable than the headache for which it was given. At the other end of the scale we have to decide what degree of toxicity can be tolerated in drugs to be used in the treatment of terminal cancer patients.

Another problem in the toxicology of drugs is somewhat peripheral to the scientific phase and yet is basic in determining whether or not the drug is to be made available to the patient. This is the matter of cost. The cost of toxicity testing has risen steadily both as a part of inflation and as a result of the newer concept of what constitutes an adequate toxicologic investigation of a new drug. It may preclude the development of drugs which will have a limited market, as for example those for the treatment of a rare disease. One of the more

poignant tragedies of drug development is the discovery during clinical trials of a small group of patients greatly benefited by a drug which on the whole gives very disappointing results. Since the sales potential of the drug cannot justify the additional toxicity studies which would be necessary before it could be marketed, it must be abandoned and the situation explained as well as possible to the patients who have come to rely on the drug.

TOXICITY IN COSMETICS

In the field of cosmetics there are fewer problems of methodology, chiefly because the types of toxicity are more limited. In their place we have problems of enforcement which arise from a peculiarity of our law which, in contrast to foods and drugs, does not require that cosmetics be tested for safety before they are sold to the public. The following examples are illustrative of the problems which arise.

Cosmetic injuries may result from either local or systemic toxicity or both. Our food and drug records show that the majority of cosmetic injuries are the result of local toxicity—namely primary irritation, sensitization or 'skin fatigue.' The dermatological literature is replete with contradictory statements regarding the local injurious effects of cosmetics, particularly with reference to sensitization. It is most difficult to evaluate the significance of sporadic reports of injuries by physicians and medical authors, since it is often impossible to correlate the incidences with extent of exposure in the general population.

The number and nature of substances which may comprise a cosmetic formulation may be most complex. However, for a number of specific reasons, surface-active agents are included in many such formulations. It is important that the limits of tolerance of these agents for the skin (both intact and damaged) as well as for eye mucosa be predetermined before inclusion in the final formulation. It was recently necessary to withdraw from the market a hair-waving preparation in which the neutralizer, when it accidentally reached the eye mucosa, produced serious acute injuries. These injuries resulted from the presence of surfactants in the neutralizer.

Most surfactants are complex condensation products of no fixed chemical composition. They are characterized by their physical properties and are broadly classified on the basis of their ionizing characteristics as anionic, cationic, and nonionic agents. Their toxicological properties vary greatly, and although there is considerable overlapping, their general order of toxicity is cationic > anionic > nonionic (2, 6).

*Hair-waving preparations.* The active ingredients of hair-waving preparations must be capable of producing chemical and physical alterations in the structure of the hair to permit waving (1). Any agent capable of producing such pronounced changes in the hair shaft may also profoundly affect the epidermis itself and even produce systemic effects in the event of sufficient percutaneous exposure (4, 5).

The majority of hair-waving preparations today are mercaptans, usually salts or derivatives of thioglycolic acid. A review of our files on reports of injuries from these preparations reveals that approximately 80% refer to a dermatitis not unlike that which would result from a simple chemical burn. An occasional report is received in which there is claimed some circumstantial evidence of a possible relationship between the use of a hair-waving preparation and blood dyscrasias. Animal experimentation in our Skin Toxicity Branch has failed to produce evidence that such a relationship does exist. The fact that millions of units of this product are used annually would further justify the conclusion that blood dyscrasias in users are purely incidental.

*Depilatories.* As in the case of hair-waving preparations, the majority of depilatory products today are also mercaptans, and usually salts of thioglycolic acid. As a rule, less soluble salts of thioglycolic acid are used, but in higher concentrations than in the waving preparations. Injuries, when such occur, are also dermatitides resembling simple chemical burns.

Incidences of a true cutaneous sensitization from the use of thioglycolates are relatively rare.

*Hair dyes.* It is unfortunate that no satisfactory substitute has been found to replace the paradiamino benzenes and aminophenols as compounds to impart a relatively permanent dark shade (especially black) to the hair. Reports of sensitization to para-type dyes are fairly numerous, approximately 24% of sensitizations due to cosmetics (8, 9). This high incidence of sensitization occurs in spite of the provisions in our Act for a mandatory patch test prior to use. As in the case of thioglycolates, an occasional report is received linking the use of para-dyes with blood dyscrasias in users. Attempts by our Skin Toxicity Branch to produce blood disorders in laboratory animals have been unsuccessful.

Hair dyes can be extremely damaging to eye mucosa and in their use precautions must be taken to avoid such contact. Our Act specifically provides for the use of potentially dangerous hair dyes provided their label contains a warning that they may cause skin irritation, gives directions for a preliminary patch test, and warns that they must not be used on the eyelashes or eyebrows.

*Antiperspirants and deodorants.* Deodorants are preparations which mask, remove or decrease perspiration odors, whereas antiperspirants are substances which, through their astringent action, inhibit the flow of perspiration. This is a cosmetic category in which it is difficult to avoid overlapping in the drug field. A substantial number of deodorants owe their activity to bacteriostatic agents, and in the case of antiperspirants the action may be entirely a reaction with proteins in the skin blocking or interfering with the normal function of the sweat glands.

The sulfates and chlorides of aluminum, zinc and zirconium, as well as the chlorhydroxide of aluminum, are used to produce the astringent, and hence the antiperspirant effects. These salts are often used in preparations of low pH (2.5–4.0), that is, in a pH range

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which is conducive to skin irritation, especially in conditions of damaged skin. Reports of injuries from the use of antiperspirant preparations are numerous and it is evident that some individuals tolerate these preparations very poorly. However, the majority of injuries from use are the results of primary irritation or 'skin fatigue' and rarely the result of a true cutaneous sensitization.

The introduction of zirconium salts, more particularly zirconium lactate in antiperspirant preparations has produced injuries characterized as axillary granulomas (10, 11). This represents a form of toxicity rarely associated with cosmetic use.

Anticholinergic and antiadrenergic drugs have also been proposed for use in antiperspirant preparations; however, such potent agents belong strictly in the drug field.

*Aerosols.* A significant number of cosmetic products today are dispersed as aerosols, a form of packaging in which the product is propelled by a gas under pressure. A number of relatively inert gases are used as propellants, namely certain fluorinated hydrocarbons known under the trade names of 'Freons,' 'Genetrons' and 'Isotrons', also chlorinated hydrocarbons, namely ethyl chloride, methylene chloride and others, as well as nonhalogenated hydrocarbons, propane and butane. As stated above, the propellent gases used in aerosol-packaged cosmetics are relatively inert, and if injuries result from their use, they are the result of freezing caused by placing the discharge nozzle at an insufficient distance from the body part intended for treatment.

The physical characteristics of the released spray will depend on the nature and composition of the formulation and also on the design of the release nozzle. The usual spray consists of particles which will vary from 1 to 50 microns in diameter. The smaller particles (1–10 microns), which are unimpinged in the inspired air, may readily reach the lung alveoli (3), and the toxicity problem then is augmented to include all the facets of inhalation toxicity.

*Miscellaneous cosmetics.* A number of severely toxic metal salts, namely mercury, lead, arsenic and selenium are used in cosmetics. Mercury has been employed since antiquity and is used today in bleach creams. It is a very toxic element and prone to produce sensitizations. It would be in the best interest of the cosmetic industry if this potentially toxic substance were eliminated from cosmetic use.

A number of cosmetic novelties have come to the attention of the Food and Drug Administration mainly through injury reports. Among these have been the use of carbon tetrachloride for drying hair, the use of impervious coats on finger nails and eyelids (anchoring false eyelashes), the use of dyes or other ingredients in lipstick preparations which may produce a photosensitization. Although these injuries are serious to the affected party their incidence in the general population remains low.

A final problem which may assume significant proportions in the future is the concept of producing cosmetic effects through oral administration. An example of this is the administration of 8-methoxypsoralen by the oral route to produce a suntanning in skin when activated by ultraviolet light or sunlight (7). Much remains to be elucidated on the psoralens' mechanism of action, safe dosage and carcinogenesis, as well as potential disturbances in normal skin physiology.

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# Agricultural chemicals

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THE TOXICOLOGICAL PROBLEMS confronting the manufacturer, formulator, handler and user of 'agricultural chemicals' no doubt exceed in both magnitude and variety the number of such problems, real and imaginary, confronting any other segment of the chemical industry (2, 3, 5, 29). Collectively these compounds pose most, if not all, conceivable types of toxicological problems (2, 3, 5, 8, 29, 46, 47), and the rate or nature of such actions may be materially influenced by the many auxiliary substances (5, 8, 26, 39, 42) used in their formulation.

Since the writer is not a toxicologist, it would be presumptuous indeed if he attempted to discuss the technical details of purely toxicological problems and the procedures to be followed in evaluating the toxicity of pesticidal chemicals, and since these have been well reviewed and summarized by experts (2, 3, 20, 25, 29, 47), he will confine himself to a consideration of the more practical problems as viewed by an entomologist.

It seems quite generally agreed that no toxic substances should be permitted in food or, for that matter, in the human environment unless they serve a useful purpose and the amounts permitted can be held to a level that will not endanger the public health (18, 20, 25). Some would qualify this generality to provide for the taking of calculated risks where the benefits derived far exceed the hazards involved (2, 10, 31, 46).

Since a considerable portion of the lay public and at least a few scientists of unquestioned integrity and competence in their respective fields of specialization believe that pesticides serve little or no useful purpose, a word on the justification for their use is a necessary prelude to any discussion of the toxicological problems involved.

Since the justification, or rather the necessity, for pesticide usage has been clearly established in the 1950 Food and Drug Administration hearings, in testimony before congressional committees and in numerous recent papers (2, 13, 20, 29, 31, 35), it should not be necessary to belabor this point here. Suffice it to say that "our man-made noxious environment" involves both biological and chemical factors. From time immemorial man has been in direct competition with noxious organisms of many types. As man has modified the environment in which he lives to suit his own needs for food and shelter, he has inadvertently created an environment highly favorable for his many competitors, often referred to as pests (13, 31, 43).

All too often he has unwittingly transported many of these species to far distant lands where, freed from the pressure of the natural control factors of their native habitat, they have become major problems. Today he must engage in a never-ending battle with a whole host of species that compete for the crops he grows and the stored fruits of his labor, and that attack his livestock, the clothes he wears, and even the building in which he lives. Opinions to the contrary notwithstanding, it was only after available biological, cultural and mechanical control measures by themselves were found to be entirely inadequate that science began to use chemical pesticides as a part of their pest control practices. Even so, "in most instances biologists are prone to regard the use of chemicals—insecticides, fungicides, acaricides—as emergency or fire-fighting methods to be used largely where appropriate ecological methods have not been developed or have not been properly applied" (11). Today all experts who know whereof they speak, whether they be agriculturists or public health officials, recognize pesticides as weapons essential to man's continued success in his battle for survival. As the Food Protection Committee of the National Research Council (18) has observed, "The maintenance and improvement of the present nutritional status of the American public is contingent upon the continued production of an adequate food supply. Plant and animal pests rank among the foremost causes of food destruction, food deterioration and food contamination. Hence, the absolute necessity for protecting growing crops and produce from serious attack by insects, plant diseases and other pests is recognized as essential from the standpoint of both quantity and quality of the food produced."

While it is true that science is continually opening new doors and it is always possible that important new procedures (30, 32, 44) for the nonchemical control of pests may be imminent, until such significant breakthroughs become proven and practical substitutes, man has no choice but to continue the use of pesticides.

Perhaps it should be noted that the first significant use of insecticides was initiated by Midwestern farmers (41) engaged in a winner-take-all combat with the

Colorado potato beetle. In desperation they tried everything available, including a readily available paint ingredient called Paris green, and when it proved highly successful, scientists were forced to reluctantly follow their lead. As a matter of fact, the entomologists were among the first to point out some of the hazards involved, and then, as now, they devoted much attention to making the use of chemicals as safe as possible. As evidence of their lack of enthusiasm for chemicals one might recall that for many years the professional entomologists and plant pathologists who left educational institutions to accept employment in commercial companies were regarded as outcasts, if not, indeed, traitors, to true science. In the years that followed, as legislative and administrative regulations were imposed on the use of pesticides, some of which seemed to be unduly restrictive, the allegiance of scientists involved in plant and animal protection from pest ravages was at least in part shifted to the side of the farmer and to the defense of pesticide usage.

Today over 200 chemicals possessing one or more pesticidal properties are currently used in the formulation of a wide variety of insecticides, fungicides, rodenticides, nematocides, herbicides and other pesticides. In all, about 7,000 formulations and over 40,000 individual brand-name products have been registered with the United States Department of Agriculture (personal communication from J. C. Ward).

Some pesticidal chemicals are extremely toxic to many classes of the higher animals, including man (5, 33, 39, 45). For example, nicotine, lead arsenate, mercuric chloride, dinitro-ortho-cresol, strychnine sulfate, parathion, endrin, and potassium cyanide all have acute toxicities in the range of 2 to 100 mg/kg. Many of these likewise have high or relatively high subacute and chronic toxicity ratings, but these values are not necessarily directly or closely correlated with acute toxicity ratings. Other pesticidal chemicals are relatively nontoxic to higher animals, e.g. rotenone, methoxychlor, piperonyl butoxide, pyrethrins and DDT have acute toxicity in the range of 250 to 10,000 mg/kg, as well as relatively low subacute and chronic toxicity ratings. Still others, such as sulfur and some of the copper compounds, are so low in mammalian toxicity they have been exempted from a tolerance requirement.

In the evaluation of any hazards that may be involved one must also consider the many adjuvants, solvents, emulsifiers and stabilizers used in the formulation of pesticides (5, 26, 39, 42). Many cases of poisoning attributed to DDT and related materials might well be chargeable to the solvent (8, 36). On the other hand, those who are alarmed about the high tonnage of pesticides in use today must note that in many formulations, such as wettable powders and dusts, the pesticide as purchased and used contains from 50% to 99% of an inert diluent such as talc, clay, diatomaceous earth or cellulose.

Carcinogenicity has raised its ugly head in the field of pesticides as it has elsewhere, and thus we find that two pesticides, Aramite and aminotriazole, otherwise relatively innocuous materials, cannot be permitted in food (16, 17) because under the Delaney amendment to the food additive amendment to the Food, Drug and Cosmetic Act, no tolerance can be established for a substance shown to be carcinogenic to any animals by oral intake.

Toxicity problems posed by agricultural chemicals involve practically all plant and animal life. The herbicides and plant growth regulators, of course, are chosen on the basis of their effect on plants, whereas most other pesticides must be nontoxic to plant life, or at least reasonably so. On the other hand, a few individuals having some specialized interest are almost certain to become alarmed if a pesticide adversely affects any species of the animal kingdom other than the one it is applied to control. Thus, in the development of pesticides the research worker must consider the candidate product's toxicity to soil organisms of all types, beneficial insects, reptiles, birds, game animals of all types, domestic animals and man. While some toxicological data are available for a wide range of species, the preponderance of such data pertain to insects and the usual laboratory animals.

Inherently the most reliable indices of toxicity are stated as mg/kg of body weight for the test animal, but pesticide residues and much of the data on rates of toxicant intake are stated in terms of parts per million of chemical on the product or in the diet. In attempting to extrapolate data from one species to another, or even from young to mature specimens of the same species, workers often fail to note that the rate of food intake in terms of body weight varies greatly with the size and rate of growth both within and between species. Thus, if insects, mice, rats, sheep and steers all received a diet containing 1 ppm of a toxicant in terms of mg/kg their rates of intake would be in the order of 1.0, 0.15, 0.05, 0.04 and 0.03, respectively. Assuming they were equally susceptible to the toxicant and 1 ppm was the amount required to kill the insect, it would take 7, 20, 25, and 33 ppm, respectively, to kill the other species. The preceding assumption is fallacious, of course, because it is well known the toxicity of chemicals varies greatly from species to species (13, 14, 27, 39) and within species, depending upon the age, sex and physiological conditions of the individual concerned.

The problems are further complicated by the fact that many pesticides may be readily acquired through more than one of the common routes: ingestion, skin absorption and inhalation. Small animals such as birds and rodents and larger domestic animals such as sheep and cattle, although inhabitants of the same treated meadow, are subjected to entirely different degrees of exposure, which makes direct comparisons between species difficult if not impossible (20, 33). In some cases the storage of pesticides in tissues creates an unanticipated food chain problem detrimental to the final predatory species (4, 39). Furthermore, many of the conditions encountered in the field cannot be adequately duplicated

in the laboratory, and therefore the over-all effect of pesticides on many species can only be determined in the field. Unfortunately, any serious adverse reactions encountered in such experiments soon become common knowledge, and the experimentor and his associates are subjected to merciless criticism. Even worse, the incident will be repeatedly cited in literature (30) as if it had occurred under approved practices rather than under experimental conditions.

Since man may also acquire some insecticides by two or more routes, he must be about equally concerned with food contamination problems and common operational or industrial hazards. Fortunately, however, materials such as tetraethyl-pyrophosphate and parathion which rank high in acute toxicity and therefore present the greatest operational hazards are relatively short-lived, and the most persistent materials such as DDT and methoxychlor, which are most apt to leave residues, have appreciably lower acute toxicities. Thus it is often possible, by exercising a choice of materials, to largely eliminate one or the other of these problems. Unfortunately, however, the grower gets such conflicting advice on the subject that he hardly knows which way to turn. Add to this the fact that many pesticides, notably some of the chlorinated hydrocarbon insecticides such as aldrin, dieldrin and DDT, have relatively high propensities for storage in animal fat and secretion in milk (24, 29), which, in view of the present Food and Drug Administration stand on milk, largely precludes their use on feed or forage crops, and you begin to get some idea of the practical problems confronting the farmer and the reasons why he may make occasional mistakes.

Some pesticides are highly stable, whereas others are readily converted to other compounds on or in plants (23), soils (22), or animals (1, 9). In some cases the conversion products are more and in other cases less toxic than the parent material. They may be more or less persistent or have a higher or lower propensity for storage in fat. These are, of course, purely chemical problems, but they have a direct bearing on the evaluation of the toxicological problems involved.

In some respects the use of agricultural chemicals is confronted with psychological prejudices (10, 25, 29, 35) that actually far exceed their toxicological hazards. Toxicologists and pathologists are confronted with the impossible task of proving the negative, but since toxicity is relative, absolute safety is not an entity that can be clearly established. Many experts have rather definite ideas as to what is safe and what is probably unsafe, but they may be reluctant to take a definite stand short of infinity. Pseudoscientists, on the other hand, have no scruples against setting forth a lack of safety through inference and innuendo. All too often their cases are built on half-truths or the misinterpretation of facts. Usually they fail to recognize that, as the Food Protection Committee (18–20) and others have repeatedly pointed out, toxicity and hazard are not synonymous. At times they readily condemn a material solely on the basis of its acute toxicity per se without giving a thought to such all-important factors as dosage rate, formulation, manner or time of application, and persistence. In other instances they assume that, because when applied in soil or to an absorbent wall surface in large amounts a material will continually kill insects for weeks or even years, its residues are equally persistent on plants. They fail to note that insects are highly susceptible, that in soil they are continually exposed through all three routes of intake and that insects often consume food equal to their body weight daily.

The agriculturists are frequently accused of using the human race as guinea pigs, which is by no means true. They have consistently endorsed and supported the establishment of reasonable tolerances based on sound scientific data, for they and their loved ones are also a part of the consuming public. They do contend that since tolerances are based on chronic toxicity studies involving life span or at least long-time feeding studies, the occasional ingestion of some one item in the diet bearing a residue slightly above or possibly well above the established tolerance will not endanger the life or health of an individual. True, such products are illegal and should not be condoned, but occasional incidents do not pose a public health problem. Be that as it may, one wonders if present-day pesticide residues can possibly do as much damage to human health and well-being as does the state of hysteria that has been created in the United States through ill-advised publicity and sensational journalism. What about hypertension as a factor in nervous disorders and heart ailments, malnutrition resulting from failure to eat certain foods, or faulty digestion and assimilation attributable to apprehension and an ever-present fear that poison abounds in every morsel of food placed on the table?

In any discussion of the toxicological problems associated with pesticides, it seems only fair that such problems and such hazards as may exist should be placed in a proper perspective (5, 25, 29, 35) with regard to other comparable problems and hazards. If we regard pesticides as chemical tools, they have a better accident and fatality record than the mechanical tools used on the same farms (40). Even in the chemical field, they have a much lower accident rate than drugs, household chemicals, solvents and miscellaneous poisons (7, 29, 42). It is also interesting to note that even within the field of pesticides between the years 1949 and 1955, 84% of the accidental deaths attributed to insecticides were induced by materials in common use prior to the advent of DDT, and only 16% of such deaths were attributed to all of the newer chlorinated hydrocarbon and organic phosphate insecticides combined (7) which are the ones most criticized and most condemned in scare stories. Arsenicals, the oldest of the insecticidal chemicals, were charged with 299 of the 518 such deaths compared with only 79 charged to all of the insecticides introduced since 1946. Furthermore, the latter were far exceeded by the 218 attributed to three rodenticides (7) in common use for many years.

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As an illustration of biased and inconsistent public sentiment, millions of Americans who smoke one or more packs of cigarettes daily, despite all the adverse publicity cigarettes have received, refused to eat even one small helping of cranberries on Thanksgiving Day because there were apparently 4 chances in 100 they might be slightly contaminated by a chemical which reportedly produced malignant tumors in rats when consumed in sizable amounts in their daily diet over a period of 2 years.

Because most agricultural chemicals are used as pesticides, they are generally assumed to be highly poisonous, and wherever they are used there is a general tendency for the public, including some physicians and veterinarians, to attribute deaths and any unusual illness that may occur in man or beast to the pesticide used. This is true despite the abundance of data to show that laboratory and domestic animals have consumed in their daily diets for months far greater amounts of the chemical than they could possibly acquire as a result of any recommended field treatment without showing any ill effects (6, 10, 24) and that epidemiological studies (21) and observations made on workers on farms (28, 37, 38) fail to show cause for alarm.

It is conceivable that the ingestion of small or even relatively large amounts of some pesticides might have beneficial effects on many species, including man, but adhering to the assumption that in chronic toxicity (15) studies any deviation from the normal is to be regarded as bad leaves no place for the discovery of any such beneficial effects. In our own and many other laboratories animals fed DDT and other chlorinated hydrocarbons in amounts far in excess of normal levels for weeks or even months have consistently maintained normal health and in many cases have shown weight gains greater than those of the check animals (G. C. Decker and R. P. Link, unpublished observations). In many cases where reduced gains were observed, a check of the data showed the lower weight gains could be attributable to reduced food intake (repellent action) rather than to the toxicity of the chemical.

In five separate studies (G. C. Decker and R. P. Link, unpublished observations) involving the feeding of chlorinated hydrocarbon insecticide residues to steers in Illinois, one or more animals were found to have abscessed livers at the time they were sacrificed. It so happened that in every case these were animals from the check lot, but the mere suggestion that these materials may have some therapeutic value almost inevitably draws a quick "Now you are being facetious!" Why? What would happen if the odds 5–0 were reversed?

Then, too, in establishing tolerances, once the chronic toxicity of the compound has been established, a safety factor (15, 48) of 100 is often imposed just to make sure. In some cases this may be justified, but since the feeding tests were based on $x$ amount of chemical in the full diet continuously and since only certain items that comprise the average diet are treated and then as a rule only a fraction of that item will ever be treated in any one year, additional inherent margins of safety are superimposed on the factor applied. Thus many legitimate uses for the pesticide are precluded or unduly restricted.

Pursuing the consideration of possible beneficial effects and applied safety factors further, it may be proper to observe that if certain essential vitamins had been synthesized for the first time in an agricultural chemicals laboratory and found to have some pesticidal properties, it is doubtful if they would be permitted in foods. As has been pointed out (34), "The minimum daily requirement for vitamin A is given as 4,000 units, or 1.2 mg. Symptoms of toxicity appear in man if 100,000, or approximately 30 mg, are taken daily for a few months. This represents a margin of safety of about 25. Thiamine, with a daily minimum requirement of 1 mg, produces symptoms of thyroid hyperactivity at dosages of 17 to 40 mg, a margin of safety of not more than 40." Obviously, they could not meet the 100–1 safety margin commonly required for pesticides.

Progress in the development and evaluation of new pesticides to fill present voids and provide for the replacement of older materials as insects develop resistance to them is being retarded by the present high development costs which range from $800,000 to $1,500,000 per successful compound (S. H. McAllister, unpublished observations). Thus, fundamental research which may lead to the development of new basic principles, biochemical-toxicological laws, and possible short-cut procedures that will ultimately reduce the cost of testing procedures should rate a top priority among research needs. A practical solution of the current insignificant or practical zero residue (12, 19, 34) likewise ranks high on the list of unsolved problems. While the possibility of discovering a new law or formula that would have universal or even broad application seems fantastically remote, it should be possible to develop consistent trends and perhaps some basic principle that would hold for specific groups of compounds, modes of action, or physiological processes which would be of great benefit.

Considering the many ramifications of the problem, the urgent need for much basic research and the seemingly endless requirements for product testing and evaluation, young scientists looking for new fields to conquer may well find the toxicology of agricultural chemicals an intriguing and profitable field in which to work.

While the toxicological problems posed by agricultural chemicals are numerous and varied, they are by no means insoluble. As a matter of fact, while the cost is exorbitant, the Food and Drug Administration has already found it possible to establish safe tolerances for a very wide variety of pesticides on many crops. Experience has demonstrated clearly that it is not the use of pesticides, but rather their misuse, that has accounted for all of the unfortunate incidents that have occurred to date. Thus, in reality our immediate problem in protecting our food supply is one of education, rather than research and legislation. Again putting our

problem in its proper perspective, the record of pesticide usage has been good, perhaps unmatched in any other field. Considering the number of chemicals involved, their varied physical and chemical properties, types of formulation, methods of application, the variety of crops and their stages of maturity, unpredictable weather, and animals involved, one can hardly help being amazed that so few incidents occur. To be sure, we have had our cranberry and other minor incidents, but none has posed any real threat to the public health and in each case the cause involved misuse of the pesticide. Such incidents are deplorable and should insofar as possible be eliminated. However, the ever-present factor of human error is not confined to the use of pesticides. When a nurse inadvertently feeds boric acid to babies, railroad engineers miss signals, pilots miss landing strips, and physicians misprescribe drugs, we explain such incidents as due to human error, but we do not extend the same philosophy to the occasional misuse of a pesticide by a farmer. The point is: the misdeeds of a very small fraction of any group, in this case pesticide users, does not justify the condemnation of an entire industry or an essential practice. It seems to be generally agreed that if all pesticide users will read the labels on containers and carefully follow the printed instructions, we will have no illegal pesticide residues and no objectionable food contamination. Why not abandon the unsound condemnation of pesticides and substitute therefor an all-out campaign on 'Read the Label' and condemn those who do not?

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XUM

# Chemicals in industry

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More than fifty per cent of the products sold by the chemical industry today were not in commercial production 20 years ago, and many were not even known. Today entire industries are based on elements and chemicals which 20 years ago had no important uses (fig. 1). Ninety per cent of the estimated 4,000 drugs and pharmaceuticals now being sold were developed during the last 10 years, in the decade which produced among other things the drip-dry shirt, the squeeze-bottle and the solid propellant (6).

The population explosion has been accompanied by an even greater explosive growth in the production of chemicals (fig. 2). It is estimated that 50,000 new chemicals will be synthesized during the year 1960, and that 10,000 new chemicals and allied products will become available in pilot-plant or commercial quantity. The number of new chemicals reported in the scientific literature has become so large that a monthly journal called *Index Chemicus*, devoted exclusively to listing new chemicals, will be published in 1960 for the first time (1). Most of this new crop of chemicals will remain as museum pieces on the chemical shelves of the laboratories where they were synthesized. A number of them will be offered by the chemical industry as development chemicals. Technical literature describing these chemicals is distributed to uncover potential applications, and samples are available on request for evaluation. Technical data sheets (fig. 3) describe the chemical and physical properties of the chemicals and suggest possible commercial uses based on these properties. A chemical may show excellent promise as a cross-linking agent, a plasticizer, an antiozonant or as an intermediate for the synthesis of other chemicals. An additional statement or paragraph, usually found on the last page of the technical brochure, is entitled *Safe Handling, Precautions for Use, Toxicity Information* or *Toxicology*. This 'back-page' information has become increasingly conspicuous in technical bulletins in recent years. It is documentary evidence of the increasing awareness of the importance of toxicological information for the future development of chemicals and products. It is now generally recognized that the mammalian toxicity of a chemical may be as important for its commercial future as its solubility, pour point, viscosity or index of refraction. Although the toxicity information is usually found on the back page of the technical bulletins, it may, under certain circumstances, be cited in prominent places in newspapers and magazines, as you well know.

With these introductory remarks, I should like to discuss the role which the industrial toxicologist plays in the commercial development of chemicals. The toxicologist's basic responsibility is to protect the health of the individuals who may have contact with chemicals and to make certain these materials are safe to make, to sell and to use. He is concerned with the research chemists, plant production workers, consumers and the public in general. The responsibility of the toxicologist follows the chemical wherever it goes, beginning with the initial small amount in the chemist's reaction flask, passing through the stage of carload quantities coming out of a huge plant, and perhaps ending with a small package in a shopping bag. Fortunately, it takes time for the chemical to progress through these stages of commercial development. During this time the toxicologist may obtain the information he needs to carry out his responsibility. This interval appears to be getting shorter, however. The electronic computer and process engineering advances have made it possible to circumvent the pilot-plant stage in some processes. The pace in the development of commercial chemicals has quickened along with other phases of modern living.

If there is sufficient basic information relating chemical structure to mammalian toxicity, the toxicologist may express concern or appear complacent the moment he hears the name of a new chemical or sees the structural formula. On the other hand, the chemical may be so new and different that he doesn't have any idea what it might do to mammalian biological systems. Some of the classes of chemicals in commercial use today are shown in table 1. Many of these compounds were not even mentioned in textbooks a few years ago, and the toxicologist who saw the chemical structures for the first time had no idea at all about their toxicity. He had nothing to 'stand on,' or 'relate to' and no basis for venturing even an educated guess.

The acute toxicity of a chemical by various routes of administration is regarded as basic toxicological information. This should be obtained before samples are sent out for evaluation so that the information can be included in the technical data sheets describing the

FUNK AND WAGNALL'S
STANDARD DICTIONARY (1937)

TITANIUM
TI-ELEMENT NO. 22, AT. WT. 47.90
"A DARK-GRAY METALLIC ELEMENT FOUND IN SMALL QUANTITIES IN MANY MINERALS. IT HAS NO IMPORTANT USES."

USES OF TITANIUM-1960

| | |
|---|---|
| AIRCRAFT STRUCTURAL PARTS | FOOD PROCESSING EQUIPMENT |
| JET ENGINES | ORTHOPEDIC APPLIANCES |
| MARINE EQUIPMENT | ABRASIVES |
| CHEMICAL PROCESSING EQUIPMENT | METAL-CERAMIC BRAZING |
| GUIDED MISSILES AND ROCKETS | TEXTILE MACHINERY |
| SURGICAL INSTRUMENTS | CERMETS |

FIG. 1. Titanium uses in 1960.

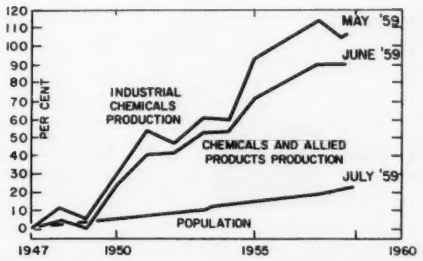



FIG. 2. Growth in chemical production and population.

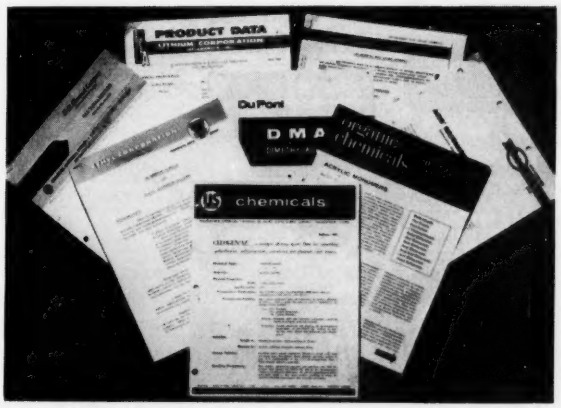


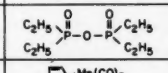
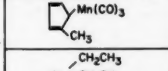
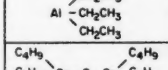
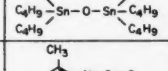
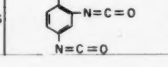
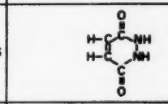
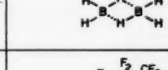
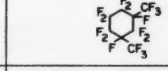
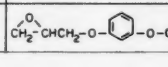
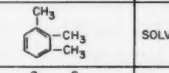
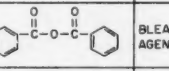
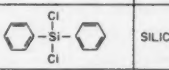

FIG. 3. Technical data sheet mastheads.

chemical. It is conceivable, even at this early stage, that the qualitative and quantitative toxicity of the chemical may present formidable obstacles to successful commercial development. Certain aromatic amines which are known to cause bladder tumors may fall into this category. Indeed, it appears that any chemical stigmatized as a 'carcinogen' will have difficult hurdles to overcome before it is used commercially.

If the chemical is to be produced in commercial quantities, additional toxicity data are needed to protect production workers in the plant who may be exposed repeatedly to the chemical. Some plants must be designed and built essentially 'molecule tight,' and elaborate engineering controls and precautions must be taken to prevent exposure to highly toxic chemicals. An extraordinary example of this is the integrated acrylate monomer plant, which processes many tons daily of three highly toxic and extremely hazardous chemicals—carbon monoxide, hydrogen cyanide and nickel carbonyl (fig. 4). Nickel carbonyl is one of the most toxic chemicals used on an industrial scale. It has the distinction of having one of the lowest threshold limits listed, .001 parts per million. More than $400,000 was spent by the Rohm and Haas Company on toxicity testing and methods for detecting nickel carbonyl (7). Two million dollars was spent for safety considerations in the design of the nickel carbonyl units in the plant. Since the plant went on stream in July 1948, there have been only four lost-time injuries due to exposure to nickel carbonyl, with no permanent disabilities.

In addition to the engineering controls and industrial hygiene practices incorporated in the plant, the determination of the concentration of nickel in the urine of the workers serves as a test of the efficacy of these

TABLE 1. *Classes of Chemicals in Commercial Use Today*

| CLASS | EXAMPLE | USE |
|---|---|---|
| ALKYL-PHOSPHATES |  | INSECTICIDE |
| ORGANO-METALLICS CARBONYL |  | ANTI-KNOCK AGENT |
| ALKYL |  | POLY-MERIZATION CATALYST |
| ALKOXY |  | FUNGICIDE |
| ISOCYANATES |  | PLASTICS |
| HYDRAZINES |  | HERBICIDE |
| BORONS |  | HIGH-ENERGY FUEL |
| FLUORO CARBONS |  | URANIUM CARRIER |
| EPOXY |  | RESINS |
| POLYALKYL BENZENES |  | SOLVENT |
| PEROXYGENS |  | BLEACHING AGENT |
| ORGANO-SILICONS |  | SILICONE RESIN |
| REACTIVE METALS | Be, Li, Ta, Ti, U, Zr | STRUCTURAL MATERIALS ALLOYS; CHEMICAL SYNTHESIS |
| RADIOACTIVE ISOTOPES | U-235, Co-60, C-14 | INDUSTRY, AGRICULTURE, MEDICINE, |

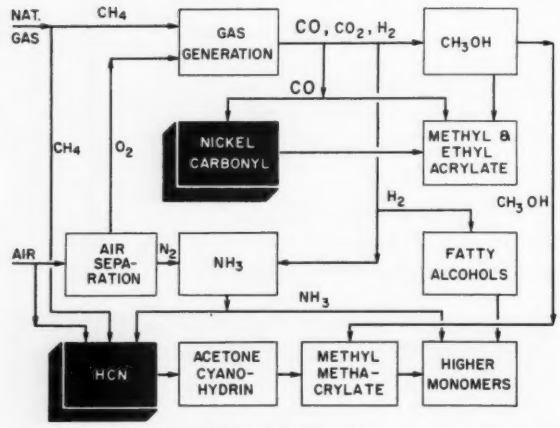



FIG. 4. Flow-sheet, integrated acrylate monomer plant.

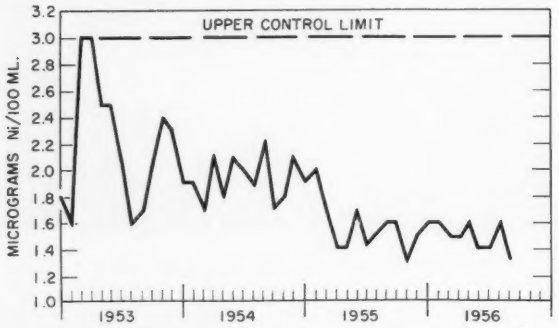



FIG. 5. Concentration of nickel in urine of workers in acrylate monomer plant. From Cummings (3).

methods in preventing exposure to nickel carbonyl (fig. 5). Urine samples of all employees subject to possible exposure are checked weekly (3).

The detection in body fluids of a chemical or its metabolites illustrates an important precautionary measure in industrial toxicology (tables 2 and 3). The presence of the chemical or its metabolites in the body fluids is prima-facie evidence that some of the chemical has been absorbed. This indicates that exposure has occurred, but does not mean that injury has resulted from the absorption of this amount of chemical in the body. By correlating clinical observations with the amount of chemical or metabolite found in biological fluids, it is possible to establish the 'biological threshold limits' for these substances. The 'exposure test' is not a test for incipient, latent or subclinical intoxication. The test for incipient toxicity is best illustrated by the blood acetylcholine esterase determination for the early detection of excessive exposure to alkyl phosphates (table 4). The development of this test has made it possible to manufacture and use potent organic phosphates as pesticides in commercial quantities.

The test for incipient toxicity represents the ultimate in precautionary measures to insure the safe use of chemicals. It is much more difficult to develop than the exposure test based on analysis of the chemical or its metabolites in body fluids since it is based on discovery of biochemical mechanisms of action. Confidence in the usefulness of a biochemical test for incipient toxicity is based on the belief that injury at the biochemical level precedes morphological cellular injury and, at this stage, is reversible simply by avoiding further exposure to the chemical.

Another approach which shows promise as a preventive measure is the early detection of abnormality of function. This is illustrated by the effects of chemical exposure on muscle output and conditioned reflex (table 5). The study of function to detect incipient intoxication has been utilized most extensively to date by industrial toxicologists in the Soviet Union (8).

The industrial toxicologist's responsibilities extend beyond the plant in which the chemical is manufactured. As stated earlier, it accompanies the chemical wherever it goes, in the community air, public water supply or food. The well-known antioxidant BHT started out as a fuel oil additive. As you know, it is now added to peanut butter, fish sticks, margarine and lard. Anti-

TABLE 2. *Exposure Tests Based on Chemical Absorbed*

| CHEMICAL | THRESHOLD LIMIT | | |
|---|---|---|---|
| | BLOOD | URINE | EXPIRED AIR |
| LEAD | 0.08 MG/L | 0.15 MG/L | |
| TETRAETHYL LEAD | 0.07 MG/L | 0.12 MG/L | |
| MERCURY | | 0.10 MG/L | |
| CHROMIUM | | 0.04 MG/L | |
| ACETONE | 50 MG/L | 100 MG/L | 0.12 MG/L |
| CARBON MONOXIDE | 3 CC% | | 0.014 % |
| HYDROGEN FLUORIDE | | 2 MG/L | |
| ARSENIC | | 0.10 MG/L | |
| CADMIUM | | 0.020 MG/L | |
| BERYLLIUM | | 0.003 MG/L | |
| NICKEL | | > 0.03 | |
| VANADIUM | | 0.030 MG/L | |

TABLE 3. *Exposure Tests Based on Metabolites*

| CHEMICAL | METABOLITES | THRESHOLD LIMIT | |
|---|---|---|---|
| | | URINE | BLOOD |
| TOLUENE | HIPPURIC ACID | 2.4 G/24 H | |
| BENZENE | PHENOL | 20 MG/24 H | |
| BENZENE | ETHEREAL SULFATE | > 30% OF TOTAL SULFATE | |
| CARBON MONOXIDE | CARBOXY-HEMOGLOBIN | | 14 % |
| TRICHLOROETHYLENE | TRICHLORACETIC | 50 MG/L | |
| ANILINE | p-AMINOPHENOL | > 10 MG/L | |
| DI-ETHYLSTILBESTROL AND PRECURSORS | ESTROGENS | > .06 μG/ML | |
| NATURAL ESTROGENS | ESTROGENS | > 6μG/24 HR | |

TABLE 4. *Test for Incipient Toxicity*

| CHEMICAL | TEST | THRESHOLD LIMIT |
|---|---|---|
| TEPP<br>PARATHION<br>HETP<br>TEDP<br>EPN<br>SYSTOX<br>DDVP<br>DIAZINON<br>DIPTEREX<br>MALATHION<br>CHLOROTHION | RBC AND PLASMA CHOLINESTERASE | 95 % OF PRE-EXPOSURE LEVEL |

TABLE 5. *Sensitivity of Criteria of Injury**

| CHEMICAL | MINIMUM CONCENTRATION (MG/L.) TO CAUSE: MORPHOLOGICAL CHANGE | CLINICAL SYMPTOMS | CHANGE IN MUSCLE OUTPUT | CHANGE IN CONDITIONED REFLEX |
|---|---|---|---|---|
| DIETHYLAMINE | 3.0 | 2.0 | 0.25 | 0.25 |
| DIOXANE | 7.5 | 5.0 | | 0.5 |
| ETHYLACETATE | 7.0 | 3.5 | 1.5 | 0.5 |
| NITROPROPANE | 5.8 | | 0.2 | 0.1 |
| TETRANITRO-METHANE | 3.0 | 2.0 | 2.0 | 0.25 |

* From Smeljansky (8).

oxidants make cake mixes possible, so that today even little girls can bake delicious cakes. It isn't necessary to tell you that before 'BHT the fuel oil additive' became 'BHT the food additive,' certain well-known feeding tests had to be carried out (4). Because such studies are time-consuming, they should be initiated as soon as it appears that a chemical will have to be proven safe as a food additive.

Since food-packaging materials are now subject to the regulations of the Food and Drug Amendment, the number of products requiring Food and Drug approval has greatly increased. The detection of minute concentrations of chemicals which have been extracted from food-packaging materials poses many challenging problems, particularly in the field of quantitative microchemical analysis. The quantitative analysis of residues of pesticides on fruits and vegetables presents similar problems. These quantitative analytical studies, in addition to the chronic toxicological feeding tests, are necessary to set tolerances for residues and safe limits of chemicals in foods.

The toxicological studies conducted on a new chemical may range from determining the effects of one dose to determining the effects of hundreds of doses. The type and the duration of the toxicological studies on a chemical depend on its proposed uses. Since biological experimentation is inherently slow, one must anticipate and plan the toxicological studies to compensate for this fact. The best way to do this is to keep in close touch with the chemists and the market development people concerned with the commercialization of the chemical.

Since the toxicologist cannot possibly test all of the new compounds synthesized each year, the best he can do is to test the most important ones and to establish correlations between chemical structure and biological activity for structurally similar compounds. The laboratory of one company alone has synthesized more than three thousand organo-metallics in five years (2). More than 4,500 fluorocarbons have been described in the chemical literature. The number of possible fluorocarbons can be estimated conservatively to exceed the one million carbon compounds which the chemist can envision (5). Until very recently, the phosphorus compounds were believed to be relatively simple and few in number. We are beginning to find, however, that phosphorus is like carbon in being capable of endless combination (9).

It must be emphasized that the methods for toxicological testing have not been standardized or prescribed in 'cookbook' fashion. This is true even for establishing the safety of chemicals in foods. Since the methodology has not been 'frozen' one is free to use his individuality and originality in the solution of a particular problem by employing the techniques of chemistry, biochemistry, pharmacology or other scientific disciplines. Toxicology is more than the routine testing of chemicals. It is biological research designed to find out as quickly as possible whether chemicals are safe to make, to sell and to use.

The most important part of toxicology is the interpretation of the experimental animal data in terms of its application to human problems. This comes with experience and judgment superimposed on sound training in the physical and biological sciences. To quote a well-known toxicologist, "You too can become a toxicologist in two lessons—each ten years long."

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# Water and atmosphere

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THE ACTIVITIES OF OUR BURGEONING POPULATIONS are fast contaminating our most precious commodities, air and water, at a rate that is alarming and to an extent that is fast becoming nationwide. Newspaper articles on air pollution are a daily occurrence in many areas; stream pollution problems are discussed with increasing frequency in news journals. Legislatures are calling for action.

To meet these challenges, stepped-up research emphasis in both areas is being provided at the local, state and federal levels; research monies are being greatly increased for investigations within the official agencies and in colleges and universities to attract researchers to help solve these complex problems. It can be anticipated that more money will be directed into these areas in the future. Oddly, some of these available research monies have gone unspent in the past for lack of research workers who were aware of the problems. But time is running out. In the interest of protection of the public health we must get more research workers into these fields.

This is the excuse I have for being here, to describe to you the major research problems in water and air in as interesting and attractive a way as I can.

## TOXICOLOGIC PROBLEMS IN WATER POLLUTION

I will describe first the major research problems in stream pollution. There are three major areas of concern: *1*) the chemical synthetics, *2*) accumulation of solids, and *3*) trace substances.

*Chemical synthetics.* In the first area, the chemical synthetics, the chief reasons for concern are their number, their structural complexity and faulty metabolic behavior. Table 1 shows some of the types of substances that are of growing concern: substances, often of great chemical complexity and variety, from the plastics industry, the petroleum industry and the rapidly growing petrochemical industry; economic poisons finding their way into our waters not only from the plant effluents but from their use in agriculture; domestically used detergents; and wastes from the paper and pulp industry, from coke ovens, from smelting and refining. Here one can see one of the greatest challenges is analysis and identification.

Adding to the challenge of identification, many of these pollutants exist in water in concentrations of parts per billion. To complicate the problem of identification further, side reaction products accompanying manufacture, as well as their products of biologic degradation, exist in the discharged wastes. I have said enough already to present a real challenge to the analytically inclined. Here is a tremendous problem. It is largely unsolved. It must be solved, for without a solution we have only substances of uncertain identity for toxicologic evaluation.

*Metabolism and mechanism problems.* Even after identification has been made, toxicologic evaluation of public health hazards is at present considerably hampered by lack of precise information on the metabolism of industrial wastes. What should the toxicologist look for in arriving at a balance between administered dose and stored and eliminated products? Almost no work in this area is in progress in this country at the present time. English workers are, however, gradually accumulating information on the metabolic products of chemical synthetics (13), but it has been only recently that sufficiently sensitive radiotracer, chromatographic methods have been applied. Table 2 illustrates the type of metabolic work being done on the chloronitrobenzenes. I select $ClNO_2C_6H_4$ because the ortho isomer has been found in the Mississippi River from St. Louis to New Orleans. Although at levels in the parts per billion range, total pollution tonnage was estimated at 40–50 ppb/day. Many towns and cities including New Orleans draw their water supply from the Mississippi River. You will note table 2 shows 13 identified metabolites and appreciable amounts (18%–37%) of unknown fate. Aromatic nitro and amine derivatives listed in the table are not well tolerated by the body.

With few important exceptions (organic thiophosphate insecticides) almost no information exists on the means by which chemical synthetics exert their toxic action. For example, the action of halogenated hydrocarbons, which embrace a large group of widely used products (solvents, fumigants, economic poisons, lubricant additives), is largely unknown. Information on the mode of action of other broad classes of chemical synthetics is equally vague. Here is a broad area of interesting toxicologic study.

*Increasing mineralization.* Problems of another sort—not

entirely man-made but related to his activities—arise from the gradually increasing mineralization of our water supplies. Giving increasing concern right now in certain areas of our country (and throughout the world!) is the question at which point will the concentration of total solids (magnesium, sulfate, chloride, nitrate, etc.) begin to show effects on health. Total solids have now exceeded 1000 ppm in some sections of the U. S., are greater than this in some parts of the world. Temporary permits are being requested to extend the limit to 1500 ppm. What limit is desirable from the standpoint of public health and practicability? These are interesting problems in electrolyte balance but may extend to other areas of metabolism. These problems are being given serious attention, but solutions will be aided by a wider and fresher approach always furnished by newcomers in the field.

Let me illustrate with a single instance an interesting problem that creates a serious threat to health of infants in certain areas of our country, first with our own well water. This is an intriguing problem for which public health officials would like to have a solution. It is the contamination of drinking water with nitrate. Such water has led to serious and often fatal poisoning in infants in which well waters were so contaminated. In 3 years, from 1947 to 1950, 139 cases of methemoglobinemia, including 14 deaths ascribed to the nitrate contamination of well water, occurred in Minnesota alone. Analyses made on the water after the infants had become poisoned usually showed values that exceeded 50 ppm of nitrate, but it is not uncommon to find many community water supplies to have nitrate values in excess of 50 ppm without poisoning cases arising. What is the reason for this peculiar, unexplained situation? Is it a bacteriologic problem in which a different type of bacteria is associated with the nitrate in farm well water that is not present in community supplies? Is it a nutritional problem whereby farm infants are fed differently? Or is it an analytic problem arising from 'after the fact' sampling of the well water? This is an important farm community problem that could be solved if given necessary attention.

TABLE 1. *Types of Suspected Hazardous Chemical Water Pollutants*

| Pollutant Types | Sources |
|---|---|
| *Cyanogenic wastes* | Plastics, polymers, resin intermediates |
| Inorganic cyanides | |
| Organic cyanides (acrylonitrile, lactonitrile, oxydipropionitrile, etc.) | |
| *Aliphatic polyamines* | Plastic catalysts |
| Diethylene triamine, triethylene tetramine, etc. | |
| *Aromatic nitro and chlorinated compounds* | Dye and chemical intermediates |
| *Aniline and aromatic amines* | |
| *Hydrocarbons, halogenated derivatives* | Petroleum processing solvent manufacture |
| All types | |
| *Metal refinery wastes* | Smelting and refining |
| Zn, Cu, Mn, Pb, other heavy metals. | |
| Radioactive wastes | |
| *Chlorinated hydrocarbon insecticides* | Agricultural chemicals |
| Toxaphene, Endrin, Aldrin, DDT, etc. | |
| *Organic thiophosphate insecticides* | |
| Phosdrin, EPN, Malathion, etc. | |
| *Herbicides* | |
| 2, 4-D, Dinitrocresol, Dalapon, etc. | |
| *Arsenicals* | |
| *Alkyl sulfates* | Surfactants |
| *Alkyl aryl sulfonates* | |
| *Quaternary amines* | |
| *Phenols, aromatics, heterocyclics* | Coke-oven quench-water |
| *Wood-pulp wastes* | Wood processing |
| Sulfides, sulfites, mercaptans | |

TABLE 2. *Excreted Metabolites of Chloronitrobenzenes (Rabbit)*

| Excreted Metabolite | Isomer Admistered | | |
|---|---|---|---|
| | Ortho* | Meta | Para |
| Ether glucuronide | 42 | 33 | 19 |
| Ethereal sulfate | 24 | 18 | 21 |
| Mercapturic acid | 7 | 1 | 7 |
| Chloraniline (free) | 9 | 11 | 9 |
| Chloraniline (conjug'd) | 0 | 0 | 4 |
| Unabsorbed (fecal) | 0.3 | 0.6 | 2.8 |
| Total accounted for | 82 | 64 | 63 |

Average values, % of dose. From Bray (4). * Found in Mississippi River from St. Louis to New Orleans (1000 miles) in concentrations of ppb.

*Lifetime effects of trace substances.* Now there is another almost entirely new and wide area of research in water quality improvement that involves substances so common to our daily existence that they have passed unnoticed as possibly influencing our health. I am referring to the lifetime effects of trace substances on health and disease as influenced by our water supplies. Why is the Public Health Service taking cognizance of this problem now? There are several reasons. The good success with supplementation of iodine in the diet and the fluoride in the drinking water supply has led to the concept that there may be other substances as yet overlooked which may in trace quantities throughout our life, or part of it, be beneficial; or conversely, there may be substances in trace amounts that, taken throughout life, may work to the detriment of man.

What is the basis for this viewpoint?

Evidence from a variety of sources, both biochemical, clinical, and epidemiologic seems to point to the possibility of certain trace substances affecting our health. I will select one substance which on present research evidence may prove beneficial to health in trace amounts. This substance is vanadium. The link I would like to

establish is between vanadium and atherosclerosis. I select vanadium because I take a little pride in the fact that it was our laboratories, while studying the toxicity of vanadium, that first showed that trace amounts of vanadium in intact animals effectively lowered serum and tissue cholesterol, and thus provided the stimulus for a great deal of additional work. The main lines of biochemical, clinical and epidemiologic evidence on this intriguing relationship are outlined below.

*Trail of Research Evidence Linking Vanadium to Inhibition of Cholesterol Synthesis and Atherosclerosis*

Vanadium increases $O_2$ uptake of fatty acids of phospholipids in liver slices (3);

decreases incorporation of $C^{14}$-labeled acetate into cholesterol of rat liver (5);

in rabbit diets, lowers plasma and tissue cholesterol on high-cholesterol diets, speeds return to normal levels, reduces aortic plaques (11);

slows deposition of cholesterol in rabbit aorta (7);

inhibits cholesterol biosynthesis by preventing mevalonic acid utilization (1);

in trace amounts, inhibits cholesterol synthesis in human intracranial tumors (2);

lowers serum cholesterol in normal men 20% (6).

Workmen with vanadium dust and fume exposure show lowered serum cholesterol (9).

Vanadium decreases urinary excretion of serotonin metabolite, 5-hydroxyindole acetic acid (10).

New Mexico has lowest incidence male mortality from coronary heart disease; New York and New Jersey have highest (8).

Vanadium present in ppb range in certain New Mexico waters; not present in waters examined in New York.

The first unappreciated clue to the biologic action of vanadium occurred in 1939 when Bernheim and Bernheim (3) showed that vanadium in small amounts altered the fatty acid metabolism in liver slices. Fifteen years or so later, independently, Curran (5) and our laboratories (11) showed that the vanadium altered cholesterol metabolism. This provided the basic evidence for the subsequent findings showing vanadium to reduce deposits of cholesterol in the rabbit aorta, and most important, vanadium's unique capacity to reduce cholesterol synthesis by preventing utilization of mevalonic acid. The chain of evidence linking vanadium with cholesterol metabolism in man and with reduction of cholesterol in normal men and in vanadium workers is outlined above.

Most recently a very suggestive piece of evidence has been reported by Lewis (10) (following a suggestion by Schroeder) of vanadium's capacity to inhibit monoamine oxidase. It is very tempting to interpret this as another important role of vanadium in regulating arterial pressure through the amine, serotonin, and possibly as an important clue to the laying down of cholesterol in arteries.

The last link important to the present discussion is a bit of epidemiologic evidence that I almost hesitate to call to your attention, namely the finding of small amounts (parts per billion) of vanadium in some waters of the states of lowest male mortality from diseases affecting the arteries, and its absence in waters that have thus far been examined in those states showing highest male mortality from these diseases. The evidence presently is very small, but it is being gathered.

I do not wish to imply that, even with all this evidence, vanadium is the only factor that may ultimately prove to govern development of atherosclerosis. The present evidence would certainly indicate an important role for vanadium in this area, however.

As to the potential effects of other trace elements in our water supplies, I will only mention a few to which attention is being given.

Magnesium is being investigated biochemically and epidemiologically, like vanadium, in its possible relation to atherosclerosis. Manganese is being investigated in its possible relationship to Parkinsonism. Heavy metals such as cadmium are being considered in their possible relation to renal hypertension, and chromium and nickel in respect to cancer; recently $Cr^{3+}$ has been identified as the glucose tolerance factor (12). Other metals in trace amounts in our water supplies are slated for study.

*Special problems.* The booming chemical industry (hundreds of millions of dollars for new plant outlay annually), ever alert to new applications of its highly competitive products, keeps the toxicologist in a constant dither evaluating the public health significance of new and untried products, or of older products for new and untried uses. Some of the problems follow.

*1)* New polyelectrolyte polymers for silt-coagulation in surface waters; anticipated use is on a vast scale.

*2)* A wide variety of new and untried compounds for weed removal in impounded waters.

*3)* Piscicides, for the riddance of undesirable fish species in impounded waters; here solvents as dispersing vehicles often pose difficult toxicologic problems.

*4)* Surface-filming agents for retardation of water evaporation for conservation of water supplies in arid areas.

*5)* A host of new antibacterial agents for treatment of swimming pool water.

*6)* Another type of growing problem requiring toxicologic surveillance is the lead contribution to surface waters (and air) from the growing number of outboard motors, now estimated at 5.2 million, that discharge leaded gas fumes under water which are in part trapped therein.

All of these particular problems have arisen in the last few years. These problems and others to come will provide enough grist for toxicologic milling for more toxicologists than are presently available. According to our recent legislation the onus is on industry to furnish evidence of safety in use where the public is concerned. Larger toxicologic staffs will be needed.

So much for toxicologic problems related to publicly consumed waters.

## TOXICOLOGIC PROBLEMS ASSOCIATED WITH AIR POLLUTION

As in water pollution, one of the biggest problems in air pollution is analysis and identification of the pol-

lutants. The substance(s) responsible for the characteristic eye irritation of oxidant smog characteristic of our urban areas in this country has still to be identified, despite much effort. We know to a fair degree the composition of combustion-engine exhaust, but far too little about the products of photochemical, chemical or catalytic interaction. New methods are needed for capturing and identifying fleeting complex radicals, molecules with short half lives in the parts-per-billion range.

Table 3 shows some types of air pollutants commonly considered to have potential effects on health. The 'oxidants' are a large, presently ill-defined group of inorganic and organic molecules possessing particular potency against living tissues, both plant and animal. Petroleum products, natural and derived from combustion, provide major concern because of *a*) cancerigenic activity of the polycyclics and *b*) their initiation of a host of reaction products. Other important groups are the metal oxides as catalysts, certain reducing gases as respiratory tract irritants, and the metals, particularly Pb, as adding to body burden of harmful metals.

Although one of the most pressing problems is the long-term effects of combinations of air pollutants, toxicologists still have a great deal to learn about the effects of single air pollutants. Among many interesting toxicologic findings in air pollution research are the facts that certain oxidants such as ozone and epoxides seem to possess radiomimetic properties, and that certain inhaled air pollutants, ozone, and carbon disulfide appear to have immunogenic properties.

Both these findings open up new, broad and unanticipated areas for interesting studies. For example, how widespread is the capacity of inhaled airborne substances to develop modified tissue components and thus generate antibodies? Will the immunochemical response be found sufficiently sensitive and specific to be useful practically to differentiate between exposures to chemical air pollutants and unrelated airborne substances such as industrial chemicals and components of tobacco smoke? In the realm of radiomimetic properties of certain oxidant air pollutants, how common is this property among this group? To what degree do they mimic the biologic action of radioactive substances?

These questions I find intensely interesting and they should repay study by immunochemists and biochemists alike who would orient themselves toxicologically.

*Effects of air pollutant combinations.* I will not discuss, further, toxicologic problems dealing with single air pollutants because of time limitation but will mention another general area in which a great deal of toxicologic study is needed and which is just starting to be explored, namely toxicologic interaction of combinations of air pollutants. One might reasonably question why simple combinations of air pollutants are in need of study at all. Why not study only the effects of over-all combinations of, say, irradiated auto exhausts or stack effluents? The reason is simply this: the materials which are combusted and which ultimately form smog, change in amount and

TABLE 3. *Recognized Air Pollutants with Potential Health Effects*

| Air Pollutants | Toxicologic Action |
|---|---|
| *Oxidants* | |
| $O_3$, NO, $NO_2$, NOBr | Respiratory tract irritants |
| Organic peroxides, peroxyaldehydes (peroxy compounds) | Radiomimetic properties? |
| Organic free radicals, air ions | Immunogenic activity? Carcinogenic activity? |
| *Hydrocarbons* | |
| Polycyclic hydrocarbons | Carcinogenic activity |
| Gasolines (olefins, br. chain sat'd) | React with oxidants |
| Oil mists (naphthenes) | Counteract effect of oxidants |
| *Metal oxides* | |
| $Fe_2O_3$, $V_2O_5$, $MnO_2$, etc. | Oxidizing catalysts producing more potent oxidants |
| *Reducing gases* | |
| $SO_2$, $SO_3$ mist | Respiratory tract irritants |
| CO | Reduces $O_2$ transport |
| $H_2S$, $H_2S_x$, mercaptans, org. disulfides | Counteract effect of oxidants |
| *Metals and metal compounds* | |
| Pb, As, Cr, etc. | Adds to body metal burden |
| *Chemical synthetics, solvents, etc.* | |

character with the passage of time. Without knowledge of toxicologic properties of the basic components and their interaction, air pollution research findings are of temporary value, requiring perpetual reinvestigation.

The basic common components of smog, therefore, should be studied in relation to their capacity to modify the toxicologic response of one another, their capacity to synergize and antagonize, so that when changes in fuels and their products occur, predictions of their public health impact may be made. From such studies it has been found already that certain air pollutants have the capacity to develop a tolerance in the host against further acute insults, not only against themselves, but against other pollutants not necessarily related in chemical structure. This is a fascinating area of investigation for those interested in the 'why' of biologic events. The mechanism by which natural resistance to toxic agents may be fortified is presently far from clear. Is it a result of adaptive enzymes (some evidence already indicates this), is it hormonal, nervous or immunochemical, or a combination of these factors? Some evidence exists that all factors may be involved.

Whenever exposures to multiple agents are concerned, the question of interaction, synergism or antagonism, is immediately raised. In air pollution this concern is particularly apt. Indeed, synergistic or exalted effects above normal expectation have already been demonstrated in a few instances, such as sulfur dioxide and formaldehyde in combination with particulate aerosols; likewise ozone and hydrogen peroxide. But a beginning has only been realized; only acute responses have been evaluated. The more important health problems are long-term effects. Much remains to be done.

Similarly, examples of antagonism among air pol-

lutants have been discovered. Hydrocarbon oil mists can counteract acute effects of certain respirable oxidants. So can certain sulfur compounds. A beginning has just been made here also. No similar attention has yet been given to the effects of combinations of air pollutants on vegetation.

I will stop here for fear I may have already created the misimpression that these problems are not being given deserved attention. They are, but the number and character of the problems are such that greater progress would be made if more researchers were attracted to these areas in water and air pollution.

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# Some problems in food toxicology

REMARKS BY THE CHAIRMAN (AFTERNOON SESSION)

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THIS COMPREHENSIVE SYMPOSIUM, which covers sources of toxic substances from the bottom of the ocean to outer space and includes our food, water and air, makes it strikingly evident that our civilization is one which so surrounds us with a host of potentially harmful substances that we must give the entire problem the most careful study. The problem cannot be solved on the emotional basis of: "It's toxic; let's avoid it." The answer can only be based on a safe level of exposure. You as scientists know that a so-called zero tolerance is a meaningless term dependent on the sensitivity of the method of measurement. Whether or not any substance is 'completely' eliminated is a purely relative term.

I would like to talk particularly about toxicological problems in connection with our food supply, since these are of such great importance to all of us. In the case of new food products, there is no emergency and no need for haste as may be in the case with a new drug needed to save lives. Furthermore, foods are used over a lifetime. Therefore, we should exercise the greatest care to see that potentially toxic substances used in foods are safe. Since there is no urgency, there should be no hasty action.

Some people still want to ask why there should be any food processing or chemicals added to foods. The benefits are obvious in conserving the food supply, lengthening the season of availibility, increasing acceptability and reducing the work of home preparation. However, there are also positive health benefits. The addition of iodine to salt, vitamin D to milk, and the enrichment of bread and flour with thiamine, niacin, riboflavin and iron have undoubtedly, through the prevention of disease, saved many lives, much disability and millions of dollars.

It must be remembered that many natural foods contain toxic substances, some of which may require processing for their removal. There is no such thing as a food supply that is completely free of toxic substances. However, our food and drug law provides only for the establishment of levels of tolerance for added substances. A difficulty arises in the definition of a safe level of tolerance. This may be particularly difficult if toxicity data are conflicting and subject to different interpretations. The natural tendency is to lean toward the side of conservatism if there is doubt. However, this is not without its consequences because unreasonably strict levels of tolerance may do serious damage to our food supply and national welfare without adding anything to the safety of the public. Thus, we now have a zero tolerance level for certain specified insecticides in milk. At first glance, everyone is inclined to shout approval, but as the tests become more refined, and more minute amounts of insecticide are detected, the strict enforcement of this regulation could seriously interfere with our milk supply and increase the price so that we must face the problem of whether it would be better to deny many children milk or allow them to get a trace of insecticide in an amount for which no human toxicity has been demonstrated.

The question of the hazard involved is further muddled by the fact that these same insecticides that are given a zero tolerance in milk are permitted with tolerance levels in the fat of beef, pork and lamb and on some vegetables and fruits. This tendency to make unnecessarily strict regulations in regard to food is not confined to the United States. The use of nitrite on some foods is permitted and has been safely used in this country for many years within the specified limits of tolerance. In England the use of nitrite for fish preservation is forbidden. Yet smoked herring treated with nitrite has been eaten for many years by millions of people without evidence of toxicity from its proper use. If toxicity tolerances are not made on a sound and reasonable basis, they will hasten the day of food shortages and higher cost of food for all of us. In 1955 about 13% of our population produced the food for the remaining 87% and created a surplus (5). The present high efficiency of U.S. agriculture relies heavily on the proper use of seed treatment, fertilizer, pesticides and insecticides. By all means, let us have protection against truly toxic amounts of both natural and added substances in our foods, but let's be sure that we are really getting protection and not needless restriction which can damage our national welfare.

The question of carcinogens is one that is particularly charged with emotion. A very great deal has been written about the cancer-producing effects of innumerable substances in many different kinds of animals. However, the fundamental fact is that the cause of cancer in man is unknown—and man has always feared the unknown. Public fear of the unknown in disease leads to hasty action on the part of authorities in order to do something to meet the public demand, even if the proper thing is not known. For example, in 1878 a yellow-fever epidemic spread through the southern United States. Memphis, New Orleans and Vicksburg were particularly hard hit. Although the cause of the epidemic was unknown, volunteers destroyed blankets, sheets and the clothing of the dead; entire houses were disinfected, quarantine measures were imposed, and a Senate committee called for tightening the quarantine. Evaders of the quarantine were shot and fires were burned at night to purify the atmosphere (2). This was a foolish waste of lives and property, now that we know that the disease is transmitted by the bite of mosquito.

Since we fear cancer and do not know its cause, when we are told that this or that substance will produce cancer in animals, our natural reaction is to say, "Let's not have any of that in our food." However, the answer is not as simple as that. Some basic nutrients have been shown to produce cancer in animals, for example, the injection of a 20%–25% solution of glucose or of a 5%–25% solution of ordinary salt (3). Yet glucose is one of the fundamental nutrients of the body, and salt is a substance without which we cannot survive.

Furthermore, cancer has been produced in experimental animals just by anoxia and also by a diet deficient in choline. In other words, an absence of something also may be carcinogenic.

Obviously, something is wrong with the theory that everything that produces cancer in animals must be banned from our food supply. When we know the cause of cancer we will be able to make an intelligent evaluation of the presently confusing data on carcinogens. Let us in the meantime try to calm the public hysteria and try to take the pressure off of our governmental officials which may lead to hasty regulations that will look as ridiculous in the future as some of our past efforts to control pestilence look to us today.

The seizure of cranberries contaminated with 3-amino 1,2,4-triazole and the attendant unfavorable publicity resulted in a two-thirds decrease in the sale of cranberries during the holidays and produced a surplus of about one million barrels. This has cost our government several million dollars and the total damage to the cranberry industry can't be evaluated at this time. My only purpose in bringing up the matter here is to question whether the aminotriazole really presented any danger of producing cancer. Astwood (1) has pointed out that Swedish turnips may be 100 times as potent in an antithyroid substance as the cranberries contaminated with aminotriazole, yet he has never traced a single case of goiter to the ingestion of these vegetables. He also points out that there has never been a case of cancer encountered in the 17 years of use of several potent antithyroid compounds. It seems most unlikely that these cranberries could have presented any hazard whatever of producing cancer in man.

The Food Protection Committee of the Food and Nutrition Board of the National Research Council has given an opinion on the general problem (4) which I would like to quote: "The foregoing review indicated that in general, substances that are potent carcinogens for one mammalian species are likely to be carcinogens for many, but not necessarily all others; and that there are graded dose responses to potent carcinogens with threshold levels of administration under specified experimental conditions, below which substances are nontumorigenic.

"The assignment of a tolerance level, or a safe level of use for man, of a demonstrated carcinogen must at present rest largely on the evaluation of alternate risk and values which usually cannot be expressed in quantitative terms."

I certainly agree with the opinion of this committee of outstanding scientists and I want to plead for the acceptance of the view that we must examine all experimental data carefully and that we must urge the establishment of reasonable levels of tolerance based on a considered evaluation of hazard and safety so that we can have both a safe food supply and a prosperous economy.

As we finish this Symposium, assailed from all directions by a multitude of toxic substances, let us not forget that we are one of the healthiest, longest-lived nations the world has ever seen. Much of this is due to the thousands of new chemical compounds which are an essential part of our health and prosperity. If we keep our emotions under control in the face of the unknown, if we can approach the problems of carcinogens and toxic substances with careful study and intelligence, the only thing that is required is the establishment and enforcement of reasonable and safe levels of tolerance.

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# Radioactive materials

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MAN-MADE IONIZING RADIATION has been a toxicological problem only since the turn of the century when the first radiation-induced burns and malignancies were being reported. Compared to lead, mercury and tar it is a relative newcomer. In this 60-year period we have acquired a large body of knowledge, especially quantitative data, about it and its effects on specific organ systems. Although our knowledge of the genetic and carcinogenic effects of radiation is far from complete it goes far beyond that which is available for a host of chemicals to which we are exposed daily in the foods we eat or in the air we breathe.

I shall limit my discussion to ionizing radiation as a toxicologic agent, not because ultraviolet, thermal and microwave radiations are free of toxic properties, but because I am more familiar with the problems associated with the ionizing radiations. The problem of controlling the hazards of ionizing radiation is a much more complex one than that for the other radiations. Except for the thermal, visible and ultraviolet radiations coming from the sun, which are readily shielded against by a thin layer of opaque material, all the other sources of these radiations are man-made and can for the most part be turned on and off at will. With ionizing radiations we not only have to contend with x-rays, the electron, proton, neutron and other radiations emitted by man-made devices which can be turned on and off, but we have the additional problem of natural (radium, uranium, thorium and polonium) and man-made radioactive materials. The latter includes the fission products produced in a reactor core, fission products and elements made radioactive by the detonation of nuclear weapons, and plutonium, americium, neptunium and other transuranic elements none of whose radiations can be turned on or off at will.

Once a quantity of a radioelement has been produced either in nature or by man it constitutes a health hazard of greater or lesser degree depending on its concentration in man and in his environment until such time as it has undergone decay to a nonradioactive state, i.e. its persistence as a hazard or as a potential hazard is dependent on its radioactive half life. This may vary from a matter of a fraction of a second up to many thousands of years. These radioisotopes, being elements, can and do, with the exception of the radioactive forms of the noble gases, get incorporated into the almost limitless variety of molecules of which our biosphere is composed.

Natural radioactivity which contributes a dose of roughly 0.1 rad per year to the organs of the body is something man evolved with and with which he prospered. Whether this radiation is essential or favorable for any or all biological systems or whether it is only another of a host of relatively minor deleterious material forces which these systems have survived is not known. It is generally accepted that natural radioactivity contributes to the total of new mutations occurring in each generation. On the other hand, statements to the effect that such and such a per cent of spontaneous mutations or of leukemias or of bone cancers result from 'background radiation' are made with very little scientific basis and belong in the realm of conjectures or speculations.

At the other end of the scale is the fact that for bacteria tens of thousands of rads radiation are lethal and for the more highly organized animals such as man and most other mammals the lethal dose ranges from 300 or 400 to 1000 r. In this lower dose range and at high dose rates there is clear-cut experimental evidence for curtailment of average life span, for leukemia induction and for induction of genetic mutation. For leukemia induction and for genetic effects there are, in addition to a wealth of data in experimental animals, data in man which tend to substantiate this statement. Furthermore, there is ample evidence in humans for cancer induction in bone and in soft tissues from doses of several thousand rads at high and moderately high dose rates. At very low dose rates—rates comparable to background—or at somewhat higher exposure rates, such as result from working within permissible levels for occupational exposure as defined by the National Committee on Radiation Protection during the past decade, there has been found no evidence in humans of harmful effects.

Insofar as observations on humans and in experimental animals are concerned, our knowledge of both the acute effect and the delayed effects produced by ionizing radiation as a toxic agent far surpasses that for most other toxic materials. This holds true for both somatic and genetic effects. We cannot state categorically that there is a level of radiation exposure below which no effect will occur. On the other hand, we can state with

considerable assurance that a single average dose of 1 r to a total population will not increase the incidence of leukemia by more than one or two cases per million population per year. The big area of doubt today in this instance, noted by the United Nations Scientific Committee in its 1958 report, is not that there may be more cases, but that there may be a lesser number or no additional cases. Similarly, a dose of 1 rad will not reduce the average life by more than a few days. Indeed in experimental animals a small amount of radiation quite regularly increases by a small amount the average life span, apparently not because of any positive effect, but rather by favoring survival in middle life in the presence of certain endemic pathogenic microorganisms. Whether (from the standpoint of a population of mice or if the experimental results were to hold true for a human population) this is a desirable or undesirable result of exposure to small amounts of radiation I leave to you.

With this as a sort of background on the state of our knowledge of radiation effects in general let me make a few categorical and general statements concerning radiation effects and then touch briefly on the problems which confront those like the National Committee on Radiation Protection and the newly-established Federal Radiation Council, who must consider guide lines for permissible exposure to ionizing radiations in a variety of circumstances.

Ionizing events occurring in biological systems produce alterations which are in the vast majority of instances deleterious to the cell or tissue irradiated. That is how radiation is used to treat cancer. These effects may be relatively subtle and require statistical methods to demonstrate as in the case where gene mutations are induced, or average life span is reduced. They may on the other hand be grossly observable as in the case of fetal abnormalities from a dose of 25–50 rads given at a high dose rate, severe illness or death from a few hundred rads whole-body exposure, or cancer from several thousand rads to the skin.

Sensitivity to ionizing radiations varies from species to species, from strain to strain and among individuals of the same strain. It takes from hundreds of thousands up to 5–10 million rads to kill viruses. Bacteria require somewhat less; tens of thousands of rads in most instances and occasionally 100,000 and more. For most mammals the $LD_{50}$ of high intensity whole body radiation is less than 1000 r. Individual strains of mice have been developed for which the $LD_{50}$ is less than 600 r and as high as 800 r. Within these strains there may be occasional individuals who may die following exposure to one-half to three-fourths the $LD_{50}$ and others who survive doses greater than half again as much as the $LD_{50}$.

There is some recovery from the acute effects of high or low doses and high or low dose-rate exposures. This, of course, is dramatically true in the case of survivors of an $LD_{50}$ dose of acute whole-body radiation. It follows also from the observation that in general an animal can survive a total dose given in relatively small increments which would have killed it if it had received the total dose in a matter of a few minutes or hours. Many thousands of rads total-body radiation can be sustained at dose rates of a few rads a day. Finally, Russell, in interpreting his data which indicate that the mutagenic effects of relatively low dose-rate exposure to spermatogonia is somewhat less than from high dose-rate radiation, has suggested that this results from some reparative process which corrects in part the initial effects of ionizing radiation on the germ cells (3).

Another generalization which holds well for somatic effects is that there is a latent period between the time of the primary ionizing events and their ultimate expression in the biological system under observation. This latent period is in inverse proportion to the total dose and to the dose rate. This suggests the concept that at very low rates the manifestation of radiation effects in an individual may be so delayed as not to occur before natural or unnatural causes of death have intervened and precluded their being manifest at all. Kohn has demonstrated that this occurs with relatively large doses at high dose rates in mice past middle life (1). In other words, departure from the normal mortality curve does not begin immediately following exposure.

Until fairly recently the toxicological problems associated with the use of the ionizing radiations have been restricted to the occupational hazards associated with the use of x-rays and radium in medicine and in industry, in the mining of pitchblende and in the effects of x-rays and radium on patients. Concern for these problems brought forth such bodies as the National Committee on Radiation Protection and the International Commission on Radiological Protection which set up recommendations for 'permissible' exposures for the guidance of persons working with x-rays and radium. These early recommendations were based on knowledge concerning the amounts of radiation which had produced grossly discernible skin changes, gross changes in the blood picture, and cancer. The idea that there was a dose of radiation which would produce no deleterious effect was taken for granted just as it has been for toxic chemicals. Only Herman Muller, beginning in the late twenties, insisted that at least for genetic effects in terms of point mutations any radiation exposure to the germ cells carried some finite probability of producing mutations. From the beginning, he was concerned with the effects of wider and wider usage of x-rays in the practice of medicine on the population's genetic material (2). This was because it was known that gene mutations when fully expressed are detrimental in by far the majority of instances. With the development of our nuclear energy program during and since World War II radiation has had to be dealt with in amounts hitherto undreamed of. Research on the effects of radiation on biological systems was greatly intensified and as knowledge accumulated the so-called permissible exposure levels for workers were decreased from 30 r/yr. to 15 r/yr. in 1949 and to what amounts to 5 r/yr. for a young radiation worker. These changes resulted from

concern over possible genetic effects on our population as more and more persons were occupationally exposed to radiation and from a fear that even for somatic effects there might, regardless of dose rate, be some statistical probability of leukemia or cancer induction from any radiation exposure, however low.

This general approach to the problem was greatly accelerated when radioactive fallout from the testing of nuclear weapons by this country, the United Kingdom and the USSR produced detectable amounts of radioactivity in the environment over and above natural radioactivity. Right now a decision is being made on how much radiation exposure is warranted to meet our medical and social needs in this nuclear age. The basic assumption being used is that radiation effects are proportional to dose regardless of how small the dose or how low the dose rate. Certainly this is not likely to lead to an underestimate of the effects of low-level environmental radiation. A determination to hold the risk of ionizing radiation to the minimum represents a striving for an ideal which a wealthy nation at peace might achieve.

Now we learn that much the same approach is being taken with respect to estimating the hazards of certain toxic chemicals released into the environment for one purpose or another. This attitude can be an extremely healthy one providing it can be broadened to include an equally intensive effort to do away with such things as the thousands of needless deaths and maimings from auto accidents and, what is even more important, the tens of millions of deaths that would ensue from another large-scale war with or without the use of nuclear weapons.

In other words, we must develop in the very near future an intelligent understanding of the hazards of the ionizing radiations, the automobile, atmospheric pollutants, water pollutants, food additives and insecticides. We must put each one in its place—in proper perspective and under appropriate controls. If we do not do so we stand a very good chance of becoming a nation of ineffective neurotics, preoccupied with morbid fears and unable to cope with what so many of us tend to pass by—the still elemental problem, survival as a people.

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# Some toxicological hazards in submarines

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A BRIEF GLIMPSE INTO THE OPERATIONAL ASPECTS OF submarines is in order, perhaps, so that we may more clearly understand the basis and nature of toxicological hazards on our modern submarines.

The World War II submarine, known as the Fleet Type, was not a true submarine but a modified surface ship which, unlike other surface vessels that submerged, had the unique capability of surfacing. The duration of submergence was directly related to the storage battery capacity which in most cases was rarely longer than 48 hours. Upon surfacing to recharge batteries the submarine atmosphere was revitalized by ventilation. Carbon dioxide concentrations, if need developed, were controlled by using lithium hydroxide powder and later pellets as a carbon dioxide absorbent.

After World War II many of the Fleet Type submarines were converted into the Guppy Class. The conversion included an intake and exhaust snorkel which furnished the submarine access to the earth's atmosphere without having to surface. This enabled the Guppy, like the Fleet Type, to adequately renew the submarine air by ventilation with outside air.

With the development of the nuclear power plant for submarines, the 'true submersible' became a reality. No longer was the submarine dependent upon the earth's atmosphere for air to run its propulsion system. No longer need it be limited to short submergences dictated by the capacity of its storage batteries. But also, no longer could man depend upon ventilation with fresh air to revitalize the ship's atmosphere. Man-made air became a necessity with all the problems attendant upon such a project. Some of the problems were obvious, as we shall see when considering carbon dioxide, and anticipatory steps were taken to meet them; some problems were suspected and dealt with when confirmed; others were identified and resolved only after considerable operational experience. Undoubtedly some problems remain to be uncovered and efforts are continually being made to identify and solve them.

Before proceeding to a detailed discussion of specific problems and means of dealing with them, it seems worthwhile to outline some of the techniques and equipment currently being used in a nuclear-powered submarine to 'purify' the atmosphere and render it compatible with human health and comfort in a sealed-cabin environment.

*1*) Air conditioning—removes some water-soluble materials.

*2*) Ventilation—helps dilute concentration in pockets to nontoxic levels.

*3*) Inert filters—remove matter entrained on dust particles.

*4*) Activated charcoal filters—absorb various hydrocarbons.

*5*) Electrostatic precipatators—remove ionizable matter.

*6*) Carbon monoxide burners—oxidize CO, H and many hydrocarbons.

*7*) Carbon dioxide scrubbers—remove $CO_2$.

*8*) Reversion to a nontoxic material—ozone reverts to ordinary oxygen.

*9*) Man—will detoxify small amounts of some toxic materials.

*10*) Control program—preventive elimination and substitution.

*11*) Surface ventilation or manifold breathing—if necessary in an emergency.

## CARBON DIOXIDE

Carbon dioxide will be the first specific substance to be discussed. As you know, it is the product of respiratory interchange and, in normal amounts, is not only nontoxic but a vital human requirement. In the closed environment of a submerged nuclear submarine the concentration if uncontrolled would rapidly reach highly toxic levels. It was foreseen that tolerable levels of carbon dioxide must be determined as well as means of maintaining such levels. Operation Hideout in 1953 established that exposure to 1.5% carbon dioxide over an extended period produced no acute signs of stress but could be tolerated for long periods of time by physiological adaptation. On this basis 1.5% carbon dioxide has been the upper limit for long cruises. At the same time it was recognized that the use of lithium hydroxide as a $CO_2$ absorbent imposed too great a logistic problem and that it would be necessary to develop a regenerative system for $CO_2$ control. After laboratory and operational testing, the present scrubber, designed at Mare Island, has been installed on all nuclear-powered submarines.

The carbon dioxide scrubber uses monoethanolamine

(MEA), a basic solution which absorbs carbon dioxide when cool and releases it when heated. The scrubber functions by passing the carbon dioxide laden air through a spray of MEA and then through a cyclone separator before returning the air to the ship's atmosphere. The MEA solution, after being exposed to the carbon dioxide for a period, is then heated in a reboiler, driving off the carbon dioxide which is compressed for subsequent disposal. The MEA is then cooled and returned to the absorber tower for further carbon dioxide absorption.

One scrubber is sufficient to maintain the submarine air at 1.5% $CO_2$ or below under normal operating conditions, which satisfactorily resolves the $CO_2$ problem. However, in solving this problem engineers have introduced a highly toxic, somewhat volatile substance into the submarine so we are faced with the MEA problem. While the concentration of MEA, as determined by a colormetric test devised by Dale Williams of Naval Research Laboratory, has always been well below the toxic levels, the potentiality of higher concentrations exist and for the future we are looking to other methods of controlling the carbon dioxide levels.

### CARBON MONOXIDE

Carbon monoxide (CO) is another contaminant which requires control equipment. There is no need to dwell upon the chemical and toxicological properties of carbon monoxide. The major source of CO on nuclear powered submarines is somewhat unusual. It is cigarette smoking, and this popular pastime accounts for about 75% to 80% of carbon monoxide production in these submarines and requires the installation of a catalytic oxidizer to maintain the CO concentration below acceptable levels (35–40 ppm). The problem was defined in the reports of Operation Hideout and confirmed during early operational cruises of Nautilus. It was known that the installed hydrogen burners would oxidize carbon monoxide to carbon dioxide, but the capacity was insufficient to maintain the carbon monoxide at the required level. As an interim measure, the hydrogen burner was modified by NRL by increasing the size, elevating the temperature and substituting another catalyst. This burner is now produced commercially by Desomatic Corporation and provides satisfactory carbon monoxide levels without restriction of smoking.

The carbon monoxide and hydrogen burner, when operated at the elevated temperature level, has another important function. It will reduce the concentration of many trace contaminants from organic sources. Most of the hydrocarbons except methane are almost completely oxidized in a single pass through the burner. The capability of this equipment for reducing the levels of many trace contaminants has led to the rather descriptive nicknames of 'atmospheric incinerator' and 'trash burner.'

Development of the carbon monoxide burner was not without complications of which one will be related. Freon used in the refrigerating and air-conditioning systems is a relatively nontoxic gas, the industrial threshold limit value being about 1000 ppm. However, Freon leaking into the submarine was found to break down in the carbon monoxide burner and form among other products hydrogen fluoride and hydrogen chloride, two very corrosive and irritating compounds. This problem was solved by careful control of Freon leaks and by adding marble chips (calcium carbonate) to the catalyst of the burner.

The oxidation of hydrocarbons by the 'trash burner' has been mentioned. The problem, however, is not solved by this reaction. The concentrations of hydrocarbons, which constitute a health hazard upon prolonged exposure, have not been precisely determined. It must also be remembered that all of the industrial threshold limit values are based upon the 8-hour day and 5-day week, whereas on nuclear-powered submarines the exposure will be upward of 60 days continuously. It is obvious that extrapolation from industrial levels would be little more than a guess, and that the time, money and effort to determine the maximum allowable concentration for all of the potential hazards is overwhelming. In addition, the acceptable concentrations are likely to be so small and the airflow through the trash burner is so low that supplementary methods of control are necessary.

The problem is being met in several ways. First by eliminating all possible sources of hydrocarbon contamination, for example by substituting water-thinned paints for paints using hydrocarbon solvents, using ethyl alcohol for cleaning, etc. In addition, toxicological studies are being done on suspect substances for which satisfactory substitutes could not be readily found. An example of this is the phosphate-ester hydraulic fluid, a rather toxic material which was shown to have a relatively low health hazard.

### PHOSPHATE-ESTER HYDRAULIC FLUIDS

The organic phosphates are well known for their toxic properties. Triaryl phosphate hydraulic fluids and lubricating oils have been introduced into nuclear powered submarines reluctantly to avoid the explosive hazard of ordinary paraffin-based oils.

Investigations at Naval Medical Research Institute and Navy Toxicology Unit have confirmed the highly toxic properties of the specific fluids being used. However, a study by LCDR. H. D. Baldridge at NMRI indicated that, in spite of the toxicity, the hazard is relatively low from vapor concentrations of phosphate-ester fluids. The potential hazard still exists, however, from the possibility of aerosol sources.

Further investigation of specific phosphate-ester hydraulic fluids is underway at Navy Toxicology Unit and, in addition, Navy Research Laboratory is developing a practical shipboard method for monitoring organic phosphates.

AEROSOLS

Of all the trace contaminants, aerosols have received the least attention until relatively recently. For this discussion, aerosols will be defined as all particulate matter, both solid and liquid, that is more or less stably suspended in air. On conventional submarines, as in our urban industrial areas for years, they were looked upon as irritating nuisances, but a closer look in both cases indicated that problems of considerable dimensions do exist.

It has been determined by Naval Research Laboratory studies that the concentration of aerosols in submerged nuclear-powered submarines reaches a steady-state concentration of about 0.4 μg/l. in approximately 100 hours. This is not only greater in average total aerosols than Los Angeles air on an average day but also compares unfavorably on the basis of chemical composition. For example, the aerosol concentration in Los Angeles averages 0.2 μg/l. of which approximately 10% is organic material, whereas submarine aerosols average 0.4–0.5 μg/l. and are approximately 80% organic substances containing a considerable amount of strongly acid materials. While little is known concerning the physiological effect on personnel of long exposure to aerosols, there is no question of their undesirability, especially from the irritating properties of aerosols, as the concentration increases. The deleterious effect on delicate instruments and electronic installations is also recognized.

The low level of concern about aerosols is evident from the fact that until recently one relatively small electrostatic precipitator was installed on nuclear-powered submarines. This was placed in the galley exhaust primarily to remove the aerosols generated by cooking. While cooking is a source of aerosols, it is quite minor compared to the amount produced by cigarette smoking.

It is perhaps fortunate that the site selected for the electrostatic precipitator was the galley because the galley, while not the chief source of aerosols, is contiguous with the crew's dinnette, the area in which the majority of smoking takes place.

In an effort to reduce the aerosol content there are several possible courses to follow. One, of course, would be to severely limit or eliminate smoking while submerged. This would probably create a morale problem of greater dimensions than the contaminant problem. A compromise of sorts would be provided by limiting smoking to certain areas. The recommended method of approach has been to increase greatly the air-cleaning capacity by installing more electrostatic precipitators.

AIR IONS

Another subject which, until recently, has received little attention in relationship to submarine habitability is that of air ions. It has, however, been recognized for years that in spite of every effort to control temperature humidity, air movement and air cleanliness, there has been a missing link that differentiates man's 'conditioned air' from nature's 'fresh air.' There are indications that space charges, created by the excess of ions of one polarity over the other constitute the environmental factor contributing to this difference.

Natural sources of air ions are cosmic rays and radioactive elements in the air and soil. In conventional submarines, the major source is from radioactive paint on dials of gauges and watches. This source has been eliminated from nuclear-powered submarines, except for inadvertant introduction of the wrong spare dial, so that the main source on these submarines is from brush discharges, high voltage discharge from sonar and electrostatic precipitators, and thermionic generation from the galley range. The number of air ions on nuclear powered submarines roughly approximates that of the atmosphere, usually less than 1000/cc, averaging about 450 positive and 240 negative ions. This relatively low air ion concentration in spite of the ample sources may be due to the high aerosol concentration which tends to immobilize and remove the ions. The air ion concentration may increase considerably when the aerosol concentration is lowered. The ion concentration is more stable in the submarine than in the outside atmosphere as the air is not affected by cosmic rays or thunderstorm activity, two of the chief causes of variation in atmospheric air. The excess of positive ions is usually attributed to the slight lower mobility of the positive ions.

Knowledge is scant concerning the physiological affect of air ions and the mechanism by which they produce their effect and even less is known about their effect upon behavior. Studies over the past 25 years, however, have given increasing evidence that the electrical characteristics of air have a subtle but definite effect upon human comfort and behavior. Some reports show that a feeling of well-being is associated with an atmosphere containing an excess of negative ions and that depressed feelings, irritability and fatigue are associated with an excess of positive ions. More specifically, medical observations indicate that an excess of positive ions may be accompanied by headaches, dizziness and faintness in addition to the symptoms above; and that an excess of negative ions may be associated with optimism, a feeling of exhiliration, relief of asthma and hayfever and an increased feeling of confidence. Physiological effects noted in the presence of negative ionization include a drop in pulse rate and blood pressure, increased carbon dioxide combining power and pH of blood, increased adrenal activity, increased growth rate and a more rapid healing of wounds and burns.

Krueger's studies at the University of California indicated that ciliary action in a rabbit's trachea is inhibited by exposure to positive ions and that this effect can be reversed by exposing to negative ions, which may be a partial explanation for the relief of asthmatic

symptoms by negative ions. Some of Krueger's more recent studies indicate that the presence of a 'normal' number of negative ions even in the presence of an excess of positive ions is effective in maintaining desirable reactions.

There are many gaps in our knowledge of this subject, but there is sufficient evidence to encourage further investigation. It is quite possible that control of air ions may contribute to submarine habitability by increasing the general comfort of the crew and help in maintaining the emotional stability and resistance to stresses from various sources.

### ATMOSPHERE MONITORING

The major constituents of the submarine atmosphere are monitored by the Mark III analyzer. This equipment was designed by NRL personnel and consists of five analytical channels, one each for oxygen, carbon dioxide, carbon monoxide, hydrogen and Freon. The oxygen channel utilizes the paramagnetic properties of oxygen, the hydrogen channel is based upon thermal conductivity and the other three channels on their infrared absorption properties.

The analyzer can sample and analyze air from all compartments of the submarine and this is done routinely at least once a watch. It is backed up by portable instruments such as the Dwyer carbon dioxide analyzer, the Mine Safety Appliance (MSA) carbon monoxide colorometric type squeeze bulb, and the Draeger kit which is a squeeze bulb and glass tube analyzer that has the capability of testing for many of the trace components in the atmosphere.

In conclusion, I will briefly mention a few of the many organizations, both military and civilian, concerned with the future efforts to identify and control the toxicological hazards on submarines. Naval Research Laboratory will continue to deal with the problems of atmosphere control by investigations both in the laboratory and on operational submarines. The Navy Toxicology Unit will continue to examine suspect materials and help to evaluate the toxicological hazard involved. The Naval Medical Research Laboratory at the Submarine Base, New London, Connecticut, will soon be investigating some of the physiological and behavioral aspects of air ion concentrations. We are also using another approach to the problem. The potential hazard from products of degradation from materials normally considered inert such as potting compounds and plastics are being studied in the chemical laboratory at Lockheed Missiles and Space Division, Sunnyvale, California.

It should be emphasized that this is a coordinated effort of these and other organizations, including the Advisory Center on Toxicology, the Bureau of Ships and the Bureau of Medicine and Surgery.

The task is a tremendous one but pioneering in the field of toxicological aspects of long-term exposures will pay off, not only in improved submarine environments but also in other sealed-cabin situations such as space vehicles.

# Space hazards[1]

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IF ANY ONE THING CAN BE SAID to have captured the imagination of man during the past several years it is the prospect of his personal exploration of space. The beginning step in what should be an endless series of explorations is now at hand and by the time this symposium is in print it is possible that both the USA and the USSR will have sent men into space for at least a few minutes or hours. The successful completion of these ventures will demonstrate that a host of intricate problems have been solved but will not mean that such trips are without hazard. Moreover, before more prolonged flights can be undertaken safely, another host of problems, many of them toxicological in nature, remain to be recognized, understood and solved.

Before entering upon a consideration of the hazards of space, it would be a good idea to settle upon the locus of the region to which we shall refer as 'space.' It is possible to demarcate space on the basis of the density or composition of the gaseous environment above the earth on the basis of the boundaries of the troposphere, stratosphere or ionosphere. For our purposes, however, an operational definition should suffice and in this sense space can be thought to begin at about 100 miles above the surface of the earth. It becomes possible to place a space vehicle in orbit at about this altitude and it is only slightly above this height that the orbit of the first manned ship of the USA is planned.

At 100 miles above the surface of the earth the density of the atmosphere is between $10^{-7}$ and $10^{-6}$ gm/m$^3$ in contrast to the value of $1.1 \times 10^3$ gm/m$^3$ at sea level (3, 7). This environment will not support life and man must travel in a sealed cabin containing all the requisites for his continued existence. While this may seem relatively simple and safe, a multitude of hazards still exist for the space traveler. Some of these arise from the contents of the space vehicle itself, while others come from the external environment. Let us first examine the latter, paying particular attention to radiations.

Since radiations are among the most easily recognized of the space hazards, there exists a substantial body (11) of useful information relating to them. Practically the entire electromagnetic spectrum (microwave, visible, ultraviolet, x-, $\gamma$- and cosmic rays) is known to be encountered in space. Since the low-energy radiations (microwave, visible and ultraviolet) are readily stopped by the envelope of a space vehicle, our chief concern will be with the more energetic radiations that can penetrate the vehicle and its occupants.

## VAN ALLEN RADIATION BELTS

During the past several years Van Allen and his associates employing data from instruments in rockets and satellites have discovered and delineated tremendous belts of radiation about the earth (12–15). These consist of an inner bean-shaped band in the equatorial region and an outer banana-shaped band extending from one auroral zone to the other. The maximum radiation intensities of the inner and outer bands are the same (ca. 40,000 particles/cm$^2$/sec.) and occur at about 2,000 miles and 10,000 miles above the earth. The inner belt begins at about 375 miles, the radiation intensity increasing with altitude to a peak whereupon it decreases to a minimum at about 5,000 miles. The outer belt may be thought to begin at about 5,000 miles, the radiation intensity increasing with altitude to a peak whereupon it decreases to a minimum at about 50,000 miles.

The major constituents of the belts are electrons of energies from 20 kev to greater than 2.5 mev. Protons of energies up to 700 mev are found in substantial amounts in the inner belt but in small numbers in the outer belt. In each belt the particles are thought to be trapped in the earth's magnetic field and to travel back and forth from one auroral zone to the other in a helical trajectory along the magnetic lines of force. At each auroral zone the particles enter regions of higher atmospheric density, collide with atoms of gas, gradually lose energy and finally become lost in the lower atmosphere. The collisions may be the source of aurora and magnetic storms. It has been proposed that particles of solar origin are injected into and give rise to the outer belt, whereas the inner belt is formed from the decay (into protons and electrons) of neutrons produced in the upper atmosphere of the earth by bombardment of its constituents by cosmic rays. There is considerable argument concerning the validity of these concepts.

[1] This work was performed under the auspices of the Atomic Energy Commission.

It has been established, however, that radiations from atomic bombs exploded at 300 miles are trapped in the earth's magnetic field (16) and that solar flares are followed by increases in radiation intensity in the outer belt (13). In order to fully assess the significance of the radiation belts further information is needed concerning the types of trapped particles and their energy spectra and concerning factors that may alter the configuration or radiation intensity of the belts. There appear to be no belts of trapped radiations about the moon (13, 17); they probably exist, however, about planets possessing significant magnetic fields.

### COSMIC RAYS

Cosmic rays fall upon the earth from all directions in space. They consist of highly energetic charged particles that are actually the nuclei of atoms from which the electrons have been stripped. Most of the cosmic rays are thought to arise within the galaxy from the radio stars, but those of the highest energy may have sources outside the galaxy. While about 99% of cosmic rays are protons and nuclei of light atoms, the remaining 1% consist of the nuclei of the heavier atoms, even as heavy as those of iron and bromine. The energies of the particles range up to $10^{19}$ ev, but the number of the particles and their energy density is small, being about 2/cm²/sec. and .333 ev/cm³, respectively, when measured outside of the Van Allen radiation belts. These levels appear to be maintained for distances further than the moon (13, 17). When cosmic rays reach the top of the earth's atmosphere they undergo inelastic collisions with the gas molecules thereby generating secondary cosmic rays. The maximum intensity of the secondary cosmic rays is at about 12 miles. Very large numbers of protons (a flux 1000 times above that of cosmic rays) have been detected at low altitudes following a solar flare (8). Apparently these energetic (*ca.* 100 mev) solar particles reach the top of the atmosphere within a few minutes or hours after the flare. (The increases in the intensity of the outer Van Allen belt mentioned above seem to be due to lower energy particles of the flare that have been traveling in magnetic clouds for about a day before reaching and colliding with the earth's magnetic field.) In order to gauge the hazard from cosmic rays further information is needed concerning their composition and energy spectra as well as the influence of solar activity upon them.

Calculations (10) indicate that man would receive dosages of 8–15 milliroentgens (mr) per day below and above the Van Allen belts and as much as 10 roentgens (r) per hour within the belts. Shielding is practical for the low-energy but not for the high-energy components of these radiations. A rough assessment of these hazards is possible when one considers that *a*) the natural background radiation is about 150 mr/yr.; *b*) the maximal permissible dosages have been set at 10 mr/wk. for the general population and at 100 mr/wk. for atomic energy workers; *c*) an acute dose of 100 r causes marked but reparable blood changes in man; and *d*) 400 r and 600 r in single doses are respectively 50% and 100% lethal for man. It would appear that space ships should spend as little time as possible in the Van Allen belts, and that space stations must orbit either above or below the belts in the regions inhabited by cosmic rays. Passage through the belts would involve receiving a dosage of a few r, but this can be avoided by launching from the polar regions.

Further attention must be given to the cosmic rays, since they may be much more hazardous than their small numbers and the above figures would indicate. For particles of a given energy the linear energy transfer in their passage through tissue is a function of the square of the charge of the particle. Thus for heavy cosmic ray particles the ionization track through tissue would be very large. For a particular set of conditions it has been calculated (9) that a core of ionization about 25 $\mu$ in diameter would be created and that the damage to tissue would be enormous. This would seem to be of considerable importance in tissues such as brain or retina which are not continuously renewed. Attempts to test these expectations have been carried out recently employing 25–100 $\mu$ diameter beams of 22.5 mev deuterons (20). It was found that the thresholds for visible lesions in mouse brain was $3 \times 10^4$ r, and $10^6$ r, for 100 $\mu$ and 25 $\mu$ beams, respectively. It was concluded that the effects of cosmic rays might not be as devastating as had been anticipated. The need for considerable exploration of this kind is obvious.

(In addition to radiation hazards arising from without the space vehicle there are also possibilities of dangers from nuclear reactors within the ship. Presently under development are reactors to be used for propulsion of space ships and for sources of auxiliary power within the ships (6). Calculations have been made of the radiation risks involved (5).)

Another significant hazard from the external environment is that of meteoroids. The danger is that the skin of the ship will be punctured as a result of gradual erosion from repeated collisions with small meteoroids or of a single collision with a larger meteoroid. While it is probable that small damages could be readily repaired, occasions might arise when ships would have to be abandoned. Provisions for safely carrying out the latter would have to be as all inclusive as those for safe travel in the space ship itself.

Possibilities for the occurrence of extremes of temperature within the space ship are several. Travel at high velocities through the earth's atmosphere on launching and re-entry will result in significant heating of the skin of the ship. The return velocities will be much greater than those of launching and the surface of the vehicle may reach temperatures of thousands of degrees C. In space, radiations from the sun may heat the skin of the ship to 100°–200°C. If the vehicle travels within the shadow of the earth and receives no solar radiation, the surface temperature of the ship may fall considerably below 0°C. In all cases except re-entry, the problem of

maintaining comfortable cabin temperatures is probably not too difficult of solution. For safe re-entry, however, provisions have to be made for the dissipation of enormous amounts of heat lest cabin temperatures incompatible with life are reached (1).

The potential for damage from the high gravity forces during the rapid acceleration and deceleration associated with launching from and returning to the earth are not insignificant. At the present time it would seem that proper orientation of the man with respect to the direction of the force of gravity will enable him to suffer no serious damage during launching. If in the future considerably greater launching accelerations are possible, other measures than positioning will have to be found in order to insure man's safety. During the deceleration of re-entry it is possible to reach gravity forces beyond human tolerance, but it is expected that this will be prevented by controlling the angle of descent and by the use of rockets to provide a gradual deceleration.

Hazards that may arise from the contents of the space ship are perhaps the least predictable and may well be among the most troublesome dangers of space travel. These hazards will be similar in nature to those already encountered in submarines (4) and will consist of the accumulation of toxic substances in recirculated cabin air. Anything that will volatilize or become abraded into fine particles in the course of time is a potential danger. The more obvious hazards are lubricants for motors and machines, refrigerants for air conditioners, volatile constituents of paints and metals (mercury, liquid sodium, cesium and beryllium) associated with nuclear reactors. While such dangers may not be formidable during short trips, they may become so in voyages lasting weeks or months. In the case of prolonged trips it will not be possible to carry conventional supplies of oxygen, water and food because of weight considerations. Provision will have to be made for inclusion in the space ship of complete cycles of water, oxygen, carbon and nitrogen, an alga or other simple plant being the key part of the system. Toxic by-products may arise in the various chemical reactions and reclamations involved in the system. The alga may even mutate to a form that is toxic for man. Bacterial contamination of both the algal culture and the general environment of the cabin might occur. Considerable attention will have to be given to the matters of personal hygiene and ordinary cleanliness.

While it is not sensible to try to touch upon all of the possible hazards of space travel, one should not close the subject without commenting briefly upon the difficulties to be encountered in the weightless state. At the present time limited information is available from experiments in which 30–90 seconds of weightlessness are produced during parabolic flights of jet aircraft. It appears that there may be difficulties in orientation, elimination of wastes and with regurgitation of contents of the gastrointestinal tract (2, 18, 19).

## CONCLUSION

Although man is about to venture into space for short periods of time and although one expects his safe return to earth, it is obvious that the hazards of space travel are manifold and great. It should be emphasized that considerable further exploration of both the space environment and the internal environment of the space ship is necessary before the dangers of space travel can be fully assessed. Among the most important efforts in these directions should be the execution of satellite experiments primarily designed for biological purposes.

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# Recognition of toxicology as a scientific discipline

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MY TITLE WAS SUGGESTED by the preface to the first issue of the *Journal of Toxicology and Applied Pharmacology* (4). I quote: "Toxicology is on the threshold of emerging into a scientific discipline of its own, for the number of problems which will require extensive toxicological research are far greater than can be resolved by those working in related fields. The responsibility of the toxicologist is greater than ever before and if he is to meet this challenge he will of necessity have to be specially trained as a toxicologist rather than acquire his knowledge of the field as a part of other scientific disciplines."

## ORIGIN OF PROBLEMS

The problems which are the responsibility of the toxicologist arise from the pressures of increasing human populations and the related increasingly complex technology. It has always been an axiom of pharmacology that any effect from a substance can be attenuated to insignificance by dilution. When there was a small total population, with but slight localized concentrations of people, the waste products of human activities were no problem. If wastes were not diffusible the population would migrate or disperse when the accumulation became obnoxious. If wastes were diffusible, the effectively infinite atmosphere and oceans, with the copious flow of rivers, would dilute them to insignificance. Today we have a tremendous and growing population, with great concentrations of people in limited areas. The environment is no longer infinite in respect to its power to dilute harmful wastes. We have increasingly urgent problems of atmospheric and water pollution.

When the population was scanty and diffuse, sustenance and comfort could be found nearby. Only rudimentary technology was required. Today's great concentrations of people cannot be supported from their immediate environs. Complex technology is required for their sustenance, health and comfort. Increased leisure resulting from the division of labor and the use of power has led us to demand comforts and conveniences. They are attainable only by bringing multitudes of chemicals into our lives. Our problems are related to, but are even more complex than, those which limit growth and lead to dissociation in bacterial colonies. Happily we have greater resources than do bacteria for the regulation of our activities toward our ultimate good. One can have faith that, when the necessity is generally understood, adequate regulation will result, partly voluntary and partly enforced by law.

The techniques of toxicology are well fitted to evaluate many of these problems of health, problems which arise from exhaustion of the diluting capacity of the environment, problems which arise from technological developments required or demanded to sustain and comfort population densities remote from their sources of nutriment. Toxicologists must recognize and study each new development and each expansion of a familiar activity. They must point out the areas where voluntary or regulatory action is required to prevent injury to health. For their conclusions to be accepted and acted upon, toxicology must be recognized as a scientific discipline.

## CHANGES IN THE CONCEPT OF TOXICOLOGY

The concept of toxicology has changed from time to time as the needs for its knowledge have changed. The word appears to have been derived from the Latin *toxicum*, meaning poison, originally a poison in which arrows were dipped. This arose from the Greek *toxikon*, pertaining to the bow. We infer that the earliest toxicologists experimented to select the best poisons for arrows, which could be relied upon for the prompt elimination of enemies. The only surviving clues to the details of this prehistoric research are the successful arrow poisons still in use by some of our forest-dwelling brothers, preparations of curare, other alkaloids and possibly the toxins of anaerobic bacteria (18). We still have activity by the cultural descendants of these first toxicologists, the small proportion of our fellows who work in secrecy for the military. They are still looking for the perfect arrow poison, or for its functional equivalent.

A concurrent interest of the earliest toxicologists must have been the elimination of personal enemies, or enemies of the state. Some probably specialized in this area. The problems of criminal toxicology are somewhat different from those of military toxicology. Less potent poisons are useful, lest prompt action is desirable, sensory detection must be unlikely. A recent historical review presents the known accomplishments of this school of toxicologists (17). Their activities may have had less popular support

than those of the military toxicologists, although the opportunity to become close to powerful leaders may have been valuable. Their cultural descendants today have fallen upon hard times. They are not generally recognized as scientists, they do not publish, and there seems to be little communication or professional feeling among them.

Increasing responsibility of the state and growing social conscience led to the need for detection of the criminal activities of the toxicologist, with an eye to prevention. The school of forensic toxicology arose, often regarded as an area of pathology. A horrifyingly engrossing presentation of forensic toxicology is that of Gonzales (11).

One of the first industrial toxicologists was K. B. Lehmann of Germany. His studies were encouraged and supported by his country's chemical industry. His work was directed primarily toward the safety of the industrial production and utilization of chemicals. Few of the substances he studied reached the ultimate consumer. Lehmann introduced the concept of *zweiphasischen* or 'two-phased' toxicity into industrial hygiene in 1911 (15). This is a combination of volatility with inhalation toxicity, hence it is an expression of the relative hazards of working with volatile substances. It is regrettable that the phrase 'two-phased' toxicity was never widely used and is no longer heard. It might clarify much muddy thinking about industrial applications of chemicals today. The concept applied to routes other than inhalation might be helpful in broadening general understanding of some modern consumer health problems.

## ENVIRONMENTAL TOXICOLOGY

These successively important areas of military, criminal, forensic and industrial toxicology account for only a minor fraction of today's toxicological research. We have no generally employed word to characterize our current work. It is concerned with foods, drugs, cosmetics, household preparations, industrial products, clothing, water and the atmosphere. 'Applied toxicology' has been used, but it is not very descriptive. 'Environmental toxicology' describes the scope of our responsibility to those who realize that our environment today is largely man-made, or man-altered.

Only by doing violence to language can one characterize most of the substances studied by the environmental toxicologist as poisons. We are exerting our ingenuity to obtain experimental injury from essentially harmless substances. Toxicology is a poor word to describe our body of knowledge. In the outsider it evokes revulsion, appropriate to the etymology of the word, not to the substances which now concern us. We are trying to determine what is safe, but the name of our discipline suggests we are determining what will kill. We badly need a new word to emphasize the positive aspects of our efforts. It must designate the quality of a substance which permits continuance of health, being neither harmful nor beneficial. Some unattractive possibilities are *impuniology*, *akeraiology*, and *asphaletiology*, the prefixes meaning without penalty, harmless, safe. These all suffer from being negatives of awkward sound. It is regrettable that all Greek words with the prefix *eu–*, meaning bland, acceptable or good, seem to have been preempted by philosophy. Eventually a positive word, inspiring no revulsion by suggested suffering or death, should become current to earn greater popular acceptance for our discipline. The name of my own research group includes the term 'Chemical Hygiene.' This term fills all the requirements and might be very useful if it received general acceptance.

Not only is the name toxicology inappropriate for the area of environmental toxicology, but there is no generally accepted description of what we try to do. It is our basic premise that there are harmless ways of utilizing substances, but that substances themselves are neither harmful nor harmless. It is quantity which causes harm. We predict whether particular ways in which men may use or contact substances will be safe, or suggest how to modify the ways to make them safe.

Our activities divide themselves into two phases. First, we discover by animal experiment the nature of the injuries which a substance can cause, and we define the amounts and patterns of intake which can result in a wide range of severities of these injuries. Second, we estimate the safe human intake from the results with animals, we predict the human intake which technological utilization will produce, and we judge whether this utilization will be safe, or we suggest how it can be made safe.

## WHAT IS A SCIENTIFIC DISCIPLINE?

Is environmental toxicology a scientific discipline today? Is it so recognized?

A dictionary definition of a science is, "A department of knowledge in which the results of investigation have been worked out and systematized; a system of ascertained facts and principles covering and attempting to give adequate expression to a great natural division of knowledge." (10).

An historian of science defines it as "ordered knowledge of natural phenomena, and the rational study of the relations between the concepts in which those phenomena are expressed," (5) and he speaks of constructing a science from the welter of phenomena, linking numerous isolated facts of the descriptive period of a science into a theoretical framework.

An experienced biologist said, "Every science begins with the observation of striking events—soon establishes rough connections between them and other events—the next stage is exact observation and measurement, with uncertainties about what should be measured—then a stage of graphs, tabulations, correlations—then an idea or concept." (12)

A definition of a discipline is "the studies collectively

embraced in a course of learning, a branch of instruction, a science, or an art." (10)

Accordingly, if today's environmental toxicology is a scientific discipline, it consists of an organized framework of theory correlating the isolated observations and experiments of the quantitative and qualitative effects of exogenous nonnutritive substances upon the human body and its functions. The framework must have been constructed from the results of specific researches which can be verified by repetition. It must be self-consistent, and it must be useful for predictions, as well as for explaining observations.

### ADVANCE ESTIMATES

Before attempting to decide whether environmental toxicology is a scientific discipline and is so recognized, we should consider in more detail the way in which the toxicologist carries out the two phases of his work. Although the steps are discussed separately, they are actually performed concurrently. There has been surprisingly little discussion of the technique employed, the rationale, and the interpretation of the results. What there is concerns chiefly substances in food. Representative of these are those of Lehman's group (14), Frazer (9) and Barnes and Denz (1). Discussion of methods and interpretations in general terms have been issued by the Food Protection Committee (7), and the Expert Committee of the WHO-FAO (22). I do not propose to discuss the methods employed in any detail but only to consider the over-all question of their status as constituting a scientific discipline.

Before any work is begun, previous experience and structural analogies give us tentative estimates of all that we expect to find out: the nature of the injuries to be expected, the intake in animals which will cause these injuries, the intake in humans which will result from technological application, and the safety of the applications.

These advance estimates, no matter how tentative they may be, guide our experimental work. At times they may be sufficient to prevent us from doing any work. The tentative human intake may be much too great for any reasonable expectation of safety, or the nature of the tentatively expected injuries may be so menacing that safety seems impossible. On the other hand the advance estimates may show the intake to be so small as to be inconsequential, insignificant, essentially zero in a toxicological sense (6). Toxicological insignificance constitutes a risk so small that no informed person can see any possible effect on public health. Only absence of a sense of proportion, only unreasonable doubt would dictate extensive experiment when possible human intake will be clearly inconsequential. As a matter of fact, these insignificant intakes may be actually beneficial, constituting the sufficient challenge upon which living things apparently thrive (19).

### QUALITATIVE ASPECTS

I look upon environmental toxicology as a form of epidemiology. It is epidemiology in reverse, prospective epidemiology. When we investigate a substance which may reach humans from their environment, either as a waste or as a technological advance, our researches are designed to answer almost exactly the questions the epidemiologist might ask when he is investigating a series of injuries. What harm can the substance cause, is it reversible or irreversible? How much will reach what fraction of the population? What are the pertinent parameters of this fraction? How frequently and over what period of time may it reach them? Will it be safe for the substance to reach the environment as planned, or will some modification in the plans be required? There is one additional question we might answer, but usually it is the product development chemist, not the toxicologist who tries to answer this. What modification in the substance may make it safer to use as planned?

Guided by analogies based on physical properties and molecular structure, we determine with experimental animals the injuries which excessive intake of the substance can cause. Excessive may refer to amount, to frequency, or to duration. We determine the mechanism by which this injury results, we determine whether it progresses or regresses when intake ceases, we usually attempt to find antidotes or palliatives. These determinations require application of all of the biological and perhaps of the behavioral sciences, such as biochemistry, pharmacology, physiology, pathology, psychology. We attempt to predict human injuries and mechanisms, but often we find that more than is yet known is required to understand fully the relationship between the experimental animal and the human.

At times we conclude that the substance produces no characteristic injury, indeed that it is not toxic in any recognized sense. The problem then is to determine why it is not toxic. It may be that the substance is so similar to a nutrient, that the enzyme systems of the body handle it as the nutrient is handled, and many times the expected human intake produces no biochemical or physiological stress. Such a finding should be a rather clear demonstration of safety. It should obviate extensive and prolonged quantitative studies. It may be that the substance in large intakes acts in some physiochemical way, such as by high osmotic pressure. Such a mechanism would be very easily diluted out, and if the effective intake is considerably above the expected human intake, convincing demonstration of the mechanism should be clear demonstration of safety.

### QUANTITATIVE ASPECTS

The quantitative part of environmental toxicology is intended to define the dosage-response curve for one or more convenient experimental animals for the particular injuries caused by the substance under study. In this we are usually forced to bow to public demands and attempt to define a 'no effect' intake. The public has a

major concern in our conclusions, and understandably wants to assume no risk from the substances it will contact. Having no real understanding of scientific principles, of the impossibility of any observation demonstrating zero, of the dosage-response curve, and no understanding of the rapidly decreasing incidence with increasing multiples of sigma, it forces us to speak in terms of 'no effect.' No real harm is done if we are not led to think also in terms of 'no effect.'

I look upon quantitative toxicological studies as a scaled-down model of the contemplated future environmental exposures to the substance under study. For a very large human population to contact the substance later is substituted a much smaller population of experimental animals, frequently rats and dogs. The difference in numbers at risk is kept well in mind. The greater homogeneity of the experimental population may be forgotten. The substance is allowed to reach the animals in a close simulation of the manner in which humans will encounter it: in the diet, in the drinking water, by contact or by inhalation. The amount allowed to reach the animals is some multiple of the amount expected to reach humans. The frequency with which the substance reaches the animals is often greater than the frequency with which it will reach humans, but the period of the experiment is usually briefer than that of expected human contact. Inhalation for 3 to 12 months, or ingestion in the water or diet for 2 years is often accepted as a reasonably practical model of a lifetime exposure of human beings. Knowledge of the biochemistry or physiology of the particular injury should determine the duration of the experiment, rather than an arbitrary rule, or the mystic belief that 2 years action in the rat is equivalent to 70 years in a human.

The use of a model in the toxicological laboratory can be a truly scientific procedure of prospective epidemiology, or it can be an unthinking acceptance of tradition, bowing to administrative expediency (1). In our usual model the chief scale-up factor is the exaggeration of the intake, with daily vs. intermittent intake a minor scale-up. The chief scale-down factors are the small model population, the greater homogeneity of this population and often the brief observation period. A factor of variable and uncertain scale effect is the difference in relative susceptibility between the model and human populations. There is much mathematical and engineering experience with the study of models, and knowledge of how to allow for scale-up and scale-down factors in utilizing the results. Toxicologists have not paid enough attention to the experience of engineers. I suspect the model is too often regarded as actually representing reality.

Experimental toxicology is flourishing like the lawn in the spring rains. Increasingly sensitive methods are being used, increasingly extensive studies are being conducted, each ingeniously devised to detect any of a rapidly expanding list of theoretically possible types of injury. A certain amount of basic work is being done to determine exactly why certain substances produce their particular types of injury. We are testing many hundreds of substances to determine how much is required to injure, and to understand the nature of the injury produced. Never has one species voluntarily done so much for the possible future benefit of another species as man is doing for the rat. It is not impossible that he will survive man. If he does so, he will find in our records all that he needs to know to prevent injury from any degree of technological civilization he cares to develop. He will have reason to be grateful to the toxicologists of the mid-twentieth century.

I believe the experimental phase of toxicology today constitutes a scientific discipline to the extent that it determines the nature of injury which a truly toxic substance can cause in experimental animals, and that it determines the degree and schedule of intake which causes this injury to a very minor extent. Experimental toxicology departs from science when it states that some lower intake is the 'no effect' intake, for no possible experimental technique can ever prove that a particular intake has no effect. We can only prove that a particular precision of observation reveals no effect. It further departs from science when it is dealing with substances which are not truly toxic, whose effects are no more than those of inert foreign bodies. Instead of trying to explain why they are not systemically toxic as we can often do by studies of metabolic pathways or physiological processes, we are likely to follow the same pattern we would use for a toxic substance and pursue such meaningless nonspecific and uninterpretable observations as appetite, organ weight or life expectancy.

Experimental toxicology also falls short of being a scientific discipline to the extent that it follows a customary path in the study of problems, rather than treating each problem as a research challenge to be approached in ways appropriate to the specific situation. Furthermore, the results of toxicological investigations are not being systematized into an organized body of knowledge. For generations pharmacologists have been denying that there is any useful relation between molecular structure and pharmacological effect. Toxicologists are prejudiced by this against attempting to codify their findings to simplify predictions about new substances, although all of us have such relationships in mind when we first see a new substance. Toxicology is still in that early descriptive stage of a science which consists of cataloging observations. The observations are not yet being fitted into an organized system, although this organization is well along in the various biological sciences which toxicology utilizes.

## EXTRAPOLATION TO HUMAN SUBJECTS

We are on less scientific grounds when we use the experimental results to estimate the safe human intake. It is common practice to consider that the human population must receive in foods, no more than one-hundredth of the amount which has no effect upon experimental animals, on the grounds that humans may be

ten times as sensitive as the animals, and that the weak human may be ten times as sensitive as the average human (13). If the utility of the substance is great, a factor less than 100 may be used; if the type of injury is particularly menacing and irreversible, a factor greater than 100 may be used. Since the factor is usually applied to the concentrations of the substance in the diet, there is actually a ratio greater than 100 between the experimental intake and the human intake judged safe, because effect depends upon molar concentrations, proportional to grams per kilo per day. No account is taken of the fact that small animals eat more than do humans. Nevertheless, I see no justification in quibbling over what the value actually should be, because it is at best an over-all guess having no relation to any one substance. It is convenient to use one standard for every substance, as long as we are unwilling or unable to determine the species ratio for each separate substance. Continued reliance on the factor of 100 gives increased confidence that it is large enough to prevent trouble, and not too large to hamper technology, although this has not been demonstrated.

Our claims to constitute a scientific discipline are weakened by our reliance on this arbitrary safety factor to mask our ignorance, or to save us troublesome work. Time after time judgments of human safety are made, substances are put into use and forgotten. No injuries are reported. The factor is hallowed by continued use, but it is not substantiated. We are making no attempt to scrutinize the results of use of each new substance to confirm or modify our original guess of 100.

In the limited field of inhalation of substances in the occupations, we have an organized program to observe them in use and to correct the estimates of safety in accord with the observations (2). A committee weighs the results of experimental work and issues an annual list of threshold limit values (3) which are advisory guides to safe working conditions. Hundreds of industrial hygienists are monitoring industrial atmospheres. A larger number of industrial physicians are following the health of workmen. Any effects that are noted are reported back to the committee, resulting in a revision downward in the appropriate threshold limit. Occasionally a prolonged study of exposure and response will prove that a limit is too low, and it will be revised upwards. This program constitutes a continuous check upon the soundness of judgments about safe occupational inhalation. We have great confidence in the validity of the list of threshold limits for their intended purpose. The essential constancy of the values over the years, under continued scrutiny, establishes the validity of the process of environmental toxicology by which they were derived (20).

Those toxicologists who are active in all areas of the environment recognize that the list of threshold limits for occupational inhalation are a unique body of toxicological information proven upon humans, not upon rats. True, the injury which some of them guard against is a purely local effect unique to the inhalation route. Systemic injury with these particular substances cannot occur except at intakes considerably higher than the threshold limit. The list of threshold limits constitutes a list of daily intakes of several hundred substances which are known to be tolerable without effect upon men. The route of entry into the body is irrevelant to systemic injury. Rudimentary physiological considerations will translate the milligrams per liter of a threshold limit to an equivalent dietary intake safe for humans. More use should be made of these data in judging the safety of other environmental exposures. This suggestion has already been made by Stokinger (21) in relation to water pollution. During a working day a man breathes about ten cubic meters of air, absorbing into his blood stream the vapors from at least four cubic meters of air. A working man may be as much as ten times as resistant as a nonworker in poor health (13). Accordingly, I conclude that four-tenths of a threshold limit expressed in milligrams per liter of air is a conservative value for the milligrams of the substance which is tolerable in the daily diet.

In no other area of environmental toxicology do we have a similarly organized program for observing the results of our judgments in order to validate them and to improve future judgments. The list of established tolerances for pesticide and food additives, to the extent that they concern toxicity, not performance of function, is a list of conservative guesses. Each successive guess is independent, following the customary path, not strengthened by known results of past experience. It might be very difficult to organize a program of observations to follow the use of a new substance in food, and I see no evidence that it has been attempted. Somewhat pertinent is a one-shot deal on the effect of intensive use of pesticides on the health of an entire area in the Mississippi region (8). In the field of pharmaceuticals such a program would be practical, but only isolated sporadic studies have been undertaken.

As I have pointed out earlier (15), it is possible to make sounder toxicological studies whose predictions can be applied without use of arbitrary safety factors. We can determine the nature of the injury an excess of a substance produces in animals. We can define an intake-effect curve for this injury and its detectable, but reversible, biochemical or physiological precursors. We can determine the human intake which results in a definite degree of the reversible precursor effect, corresponding to a point low on the intake-effect curve. Comparison of the human and animal intakes for the precursor effect will yield, in many instances, a specific ratio of susceptibilities which will give us an estimate of the safe human intake. This approach is more difficult than today's usual model, followed by use of an arbitrary factor, but it is more in accord with the practices of scientific utilization of models in other fields.

### THE FINAL JUDGMENT

Determination of the proposed human intake may be simple, or it may be complex. If we are dealing with an

airborne or water-borne waste which is already being discharged, measurements under various meteorological and flow patterns are straightforward. If the waste is not yet being discharged, estimates must be made, based on the known behavior of some other substance. If we are dealing with a technological advance which will directly add a substance to food, air or water the amounts necessary to accomplish the technical purpose are already known. If the advance only indirectly adds the substance, analytical chemistry may yield sound estimates of the amount which can reach humans. If the advance puts a new preparation in the hands of the public, estimates will be uncertain because of ignorance of the degree to which public usage will deviate from the directions for use. Another problem in estimating human intake is the increased kinds of usage which almost always follow introduction of a new substance.

The final judgment of safety consists of a comparison of the expected human intake with the estimated safe human intake. This is not a simple arithmetic comparison. One must weigh the degree of menace in the kind of injury the substance can cause and the degree to which this injury may be irreversible and progressive at the time when it will first be recognized. One must weigh other causes of this same injury which are already in the environment. One must weigh characteristics of the humans to be exposed which may make them unusually susceptible, and the probable range of susceptibilities within the exposed group. Furthermore, I feel that every scientist should consider the social desirability of his findings. One should weigh whether the proposal would be useful to society. This value judgment is far from the subject of safety, but it is an obligation of the scientist or professional man.

Only the toxicologist should evaluate the significance of his findings. If he stops when he has completed his experimental studies, he has not gone beyond the field from which he sprang, pharmacology. Then he must leave to others the unique part of his professional responsibilities, the evaluation of the safety of utilization of the substance he has studied. These others cannot possibly know all the factors which must enter into the final decision. They may be touched with the faddism which brings revulsion from all chemicals and artificial conditions, or unreasoning dread of some particular injury, or they may be touched with the blind enthusiasm of the protagonist of some particular technological development. The public, through its elected representatives, should decide policy for environmental safety in broad terms. Implementation of this policy should be left to the scientific community.

## SUMMARY

In summary, we toxicologists are honestly doing our best to solve the problems presented by exhaustion of the infinite dilution capacity of the environment through overcrowding and by the exponential increase in foreign substances presented to the populace by technological developments required for sustenance or comfort. But our toxicology is an infant, barely emerged from the womb of pharmacology. We do not fully know how to utilize our strength and talents. We use certain pragmatic techniques to estimate the harmless intake of a substance for experimental animals. Some of us have an almost religious faith in their mystic symbolism for the exposure of human subjects to the substance. We do a more rational job in determining the nature of injury to the animals, leaning heavily upon comparative physiology and biochemistry to predict the injury human beings may suffer from excessive exposure. Up to this point, toxicology constitutes a scientific discipline but has not yet reached the stage of systematizing its knowledge as more mature disciplines have done.

The interpretation of results upon experimental animals to estimate a safe human dose and to give a final judgment upon safety of use is not now a scientific procedure, although much can be done to make it more scientific.

If toxicologists want to be recognized as practitioners of a scientific discipline, the first step is for themselves to recognize toxicology as a scientific discipline. History shows they will then organize a society, establish a journal as a forum for their philosophy and controversies, hold annual meetings, and become a profession, perhaps with annual awards and even state registration. I myself would regret to see toxicology become completely a scientific discipline. I look upon a discipline as an established pattern of actions. Toxicology should never involve an accepted testing procedure. We are too close to this already. It should be a research activity. It should be an art, utilizing all of the biological sciences to obtain the facts with which it forms its judgments.

## CHALLENGES

New viewpoints, new knowledge and new data are needed to replace some of our pragmatic activities with truly scientific operations. This need should be a challenge to the newcomer to toxicology, as well as to the established practitioner. The following are some of the challenges suggested by my discussion.

*1*) How distinguish between effects which can be adequately studied in a brief period, such as narcosis, and those which require very prolonged study of our model?

*2*) Can an injury, first noted after many months intake in an animal, be produced in a short time by starting with an old animal?

*3*) How rapidly does a particular human injury arise in comparison with the same injury in a rat or dog with the same intake?

*4*) What is the significance to public health of an effect in experimental animals which does not and cannot occur in human beings?

*5*) Are MacNider's more resistant regenerated liver cells (16) a general phenomenon for all types of injuries?

Has this any bearing on the safety of intermittent intake of foreign substances?

*6*) Can the hypothesis of 'sufficient challenge' (15) be established, or is it an illusion?

*7*) Can extrapolation of the dose-response curve give an estimate of the 'no effect' intake which is sounder than any direct attempt to determine it?

*8*) Can the ratio of susceptibilities between rat or dog and human beings be convincingly demonstrated for chronically toxic substances without risk to the human subject?

*9*) How can a practical study of the use of a new substance be organized in order to evaluate the soundness of a prediction of safety and to improve future predictions?

10) Synthesize generalities (natural laws) useful for predictions from the multitude of toxicological studies made upon single substances.

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# Training of toxicologists

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TOXICOLOGY CARRIES AN UNPLEASANT CONNOTATION IN the minds of many, reflecting perhaps its ancient association with primitive witch doctors and in the middle ages with poison murderers for hire. As an emerging science, toxicology has had a status low in the scientific pecking order, although a few courageous men have spoken encouraging words, like those of Dr. Gaddum at the XIX International Physiological Congress in Montreal. In no small part the low place held by toxicology in the family of sciences today may be ascribed to the preoccupation with 'testing.' Toxicity tests are necessary, and useful, and important; the intellectual content in most toxicological testing is elementary. In the past few years, however, there has grown up a body of toxicological science, as illustrated by the Symposium on Toxicology at the 1959 Federation Meeting. The future of toxicology looks toward the development of a basic science from which will come an understanding of the manifold problems of a practical nature.

## WHAT DO TODAY'S TOXICOLOGISTS DO?

It is important at the outset to consider the diversity of activities collectively making up 'toxicology.' Even in casual conversation, any of several quite different kinds of work may be described as toxicology.

*1)* Most commonly perhaps, the branch of pharmacology related to the effects of therapeutic agents given in overdose, or

*2)* the untoward symptoms that accompany the administration of therapeutic doses of these agents.

*3)* To the physician, toxicology may mean the problems frequently arising in the practice of medicine requiring diagnosis based on the understanding of toxic effects.

*4)* To the physician practicing forensic medicine, toxicology includes tissue changes as a result of chemical or drug action,

*5)* but especially chemical analyses of tissues or fluids for substances as potential causes of poisoning. In medicolegal toxicology, expert analytical chemistry and biological acumen are put together by the medical detective.

*6)* A great branch of toxicology centers on the effects of chemicals not used in therapy. Here can be found the problems of 'nontoxicology' (Frazier), e.g. of food additives, 'nutritional toxicology' (Darby), of industrial toxicology, of economic poisons, of home poisonings, and of environmental pollution. As a part of preventive medicine, industrial toxicologists must guard against the effects of chronic exposure, learn how to detect, discover the cause of, and prevent poisonings.

*7)* Problems of chronic exposure of a sort never before imagined are posed by the atomic submarine and the space vehicle in which 24-hour exposures will be the rule, not the exception.

*8)* Radioactive fallout has added still another major class of toxic effects, with the attendant problems of permissible limits, and a new specialty of radiation biology. The future problems of controlling radioactive wastes, for example, in the peaceful uses of atomic energy stagger the imagination.

"What do today's toxicologists do?" So many kinds of jobs with such a diversity of techniques and skills that only the points of view are coincident. Toxicologists in each of these activities have as their chief concern the undersirable pharmacological responses to excessive amounts of agents.

## ON THE JOB TRAINING

The practicing toxicologists carrying on these diverse activities have been drawn almost without exception from allied sciences. A questionnaire directed to about 60 persons, many of whom are full-time toxicologists but a few of whom have only tenuous contact with toxicology, brought replies from 56. Of these, 37 hold only Ph.D. degrees, 5 hold only M.D. degrees and 6 others have both Ph.D. and M.D. degrees. Of the 43 Ph.D.'s, 15 had graduate training in biochemistry, 10 in pharmacology, 4 in chemistry, 3 in organic chemistry, 3 in physiology, 2 in industrial hygiene, 2 in zoology and 1 each in pharmaceutical chemistry, endocrinology and toxicology. No defense of the sample as authentically delineating today's toxicologist is offered; however, the broad outlines are reliable enough for the present purpose. The diversity of training reflects the diversity of activities classed as toxicology. Of these men, only one listed toxicology (forensic) as his primary field of training. It is therefore a reasonable conclusion that today's toxicologists are converted chemists, biologists or biophysicists trained on the job. The respondents were a

mature group as a whole. Most (29) of the Ph.D.'s had received their degrees in the 1930's and 40's; most of the M.D.'s (8) had received their degrees in the same 20 years.

The respondents stated that their special training in toxicology had been obtained for the most part on the job, whether in occupational health, toxicological research, postgraduate training in medicine, or experience in a forensic medical laboratory. A few special courses were listed: *a*) the Isotope Training Courses at Oak Ridge and Brookhaven, *b*) statistics, and *c*) in a few cases, special courses in toxicology.

## PRESENT-DAY INSTRUCTION IN TOXICOLOGY

Toxicological facts are presented to medical students as each therapeutic agent is discussed in the pharmacology course. In addition, formal courses in toxicology are listed in a number of medical school catalogues. In the College of Medicine of the University of Nebraska, one or two students are permitted to take an advanced toxicology course in which practical experience in the quantitative determination of poisons in human material is gained in the state toxicological laboratory. Concurrent observation of cases of poisoning in the hospital provides clinical insight. Assigned reading and discussions about the materials being analyzed or the clinical cases are included. Elective courses for medical students are offered in a number of medical schools, for the most part lecture courses, although some schools add laboratory work. Thus, the advanced course in toxicology for residents in occupational medicine at the University of Rochester has no laboratory exercises. In contrast, the introductory course in toxicology for the group of 20–30 health physics students at the same university is a full-scale laboratory course. Graduate credit courses in toxicology are offered in a few medical schools, e.g. one graduate student is registered with a major emphasis in toxicology at Indiana University. Graduate courses at Chicago, California, Miami, Pittsburgh and Harvard School of Public Health may be listed. At present, to my knowledge, however, no full-scale Ph.D. program in toxicology is functioning routinely.

The contrast is little short of amazing when the miniscule efforts in the education of toxicologists are set against the urgent need for toxicologists. How many toxicologists are needed and with what training is not at all understood. The Pharmacology Society could perform a useful function by conducting a survey of the need for toxicologists clearly foreseeable, for example, in the next 3 or 4 years. Such a listing would document the national plight.

## THE PRESENT-DAY NEED

*1*) We need forensic toxicologists. It is often stated that as high as 80% of the poisonings in this country are undiagnosed. Hospitals and medical centers need assistance in their diagnostic procedures.

*2*) We need governmental toxicologists. The safety of foods is guaranteed by the decisions of toxicologists of the Food and Drug Administration. We need research toxicologists to furnish evidence of the safety of substances that become food additives.

*3*) We need industrial toxicologists to establish safe atmospheric concentrations for the multitude of chemical substances to which working people are exposed.

*4*) We need military toxicologists, not only for security reasons, but for public health reasons. Fuels of radically new kinds used in military machines, for example, are capable of contributing large scale contamination to the atmosphere.

*5*) We need space toxicologists to fix the limits at which substances can be safely inhaled round-the-clock for days or months at a time.

## EDUCATION OF TOXICOLOGISTS OF THE FUTURE

A first step can be the widening of interests in existing Pharmacology Departments to become Departments of Pharmacology and Toxicology in medical schools, pharmacy schools and schools of veterinary medicine. In a few schools there is already sufficient activity in toxicology to justify separate division or department status. Support by Public Health Service training grants is urgently needed and can catalyze a rapid and profitable expansion. For the foreseeable future, training facilities should be inclusive and diversified rather than exclusive and concentrated. Toxicologists are needed who are primarily biologists, primarily chemists or primarily biophysicists. There is no idea that every school should try to encompass all of these fields of toxicology. Programs in toxicology should be developed that are not identical, not similar, not even overlapping. Some should have a strong emphasis in biology, and others a strong emphasis in biophysics.

## TOXICOLOGY CURRICULUM CONTENT

The necessary requirements are a good grounding in pharmacology plus research experience in toxicology.

The broad biological training can come from the preclinical medical courses; certainly the medical school courses in physiology, biochemistry and pharmacology must be required. How much anatomy, histology, bacteriology and pathology can or should be included will presumably vary from school to school.

Special seminar courses can cover topics such as economic poisons, military chemicals, heavy metal toxicology, forensic toxicology, drug law, antidotes, evaluation of toxic chemical agents, toxicological methods. Other related courses may include statistics, industrial hygiene, advanced organic and analytical chemistry, radiation biology.

Research experience must remain the heart of the graduate education of toxicologists. A nearly virgin field of great breadth can be glimpsed. Two specific areas can be pointed out:

*Descriptive toxicology. a*) Electron microscopic examinations of toxic changes in tissue; *b*) species variations in toxic response; *c*) complications in toxic actions by viruses infecting the test animals; *d*) cancer; *e*) lifetime studies.

*Mechanism and metabolic studies. a*) Injuries at biochemical levels; *b*) antagonists; *c*) isotopic studies of pathways and rates.

## RECRUITMENT

The manifold activities that toxicology encompasses require in turn that people should be sought with a variety of backgrounds in undergraduate training. A considerable diversity was discovered in the undergraduate fields of specialization of the respondents to the questionnaire referred to above. These were chemistry 34, biology 14, pharmacy 6, pre-med 2, bacteriology 2, education 2, and chemical engineering 1. Prospective students in toxicology must be sought on a broad base of recruitment. Not only premedical majors in college, but majors in chemistry, biology and physics should furnish graduate students with the breadth of interest needed.

## SUMMARY

For the multiplicity of tasks toxicologists are performing today, men must be trained with a corresponding diversity of background.

Many toxicologists are needed—how many is not known. It is recommended that the Pharmacology Society sponsor a survey to estimate the need.

Toxicologists of the future need to be trained in the same scholarly pursuits that characterize successful physiologists, biochemists or biophysicists. Graduate programs are needed. A first step can be the establishment of Departments of Pharmacology and Toxicology in schools of medicine, pharmacy and veterinary medicine. Training grants from the Public Health Service are urgently needed to catalyze this necessary development. For the Ph.D. programs, recruitment should proceed on a broad basis, drawing in graduates whose primary interests are chemistry, biology or physics.

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